The Lancet · Saturday April 29 1961

PROTEIN-LOSING GASTROENTEROPATHY IN CONGESTIVE HEART-FAILURE

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HYPOPROTEINÆMIA in patients with congestive heart-failure has been described repeatedly (Payne and Peters 1932, Ellis 1933, Thomson 1934, Herrmann 1946, Hammond and Ross 1960). Many of the earlier investigations were chiefly concerned with the possibility that hypoproteinæmia might contribute to œdema formation. In particular, there has been much interest in the relation of plasma-protein levels to chronic constrictive pericarditis, because this condition so often mimics cirrhosis of the liver in its clinical and laboratory manifestations. Hill et al. (1956) found significant hypoalbuminæmia in only one out of fourteen cases of constrictive pericarditis tested, and suggested that the albumin level might be a useful differential point. Other authors (Paul et al. 1948, McKusick 1952, Gimlette 1959, Malm 1959), however, have found hypoalbuminæmia or hypoproteinæmia in a larger proportion of such patients, ranging from a quarter to a half. Patients in whom surgical treatment of chronic constrictive pericarditis is successful recover quickly from the hypoproteinæmia, thus clearly demonstrating the causal role of the cardiac condition (McQuarrie 1942, Paul et al. 1948).

Among the possible causes of hypoproteinæmia in heart-failure, one must consider: (1) impaired protein synthesis due to malnutrition or to cardiac fibrosis of the liver (Moschcowitz 1952), (2) an exaggerated rate of loss of plasma proteins through proteinuria or internal degradation, and (3) the possibility that an increased plasma volume might cause hypoproteinæmia by dilution. In most of the published work on hypoproteinæmia in heart-failure, there are not sufficient data to permit clear distinction among these various alternatives. In recent years, however, isotopically labelled albumin has made possible precise studies of the mechanisms of hypoproteinæmia.

Bauman et al. (1955) investigated the distribution and metabolism of ^{131}I-albumin in ten patients presenting "markedly advanced and intractable congestive heart failure". Their series included several different ætiological types of heart-disease, but unfortunately did not include chronic constrictive pericarditis. Detailed clinical reports on the individual patients were not given, nor were data on extent of œdema or elevation of venous pressure recorded. In this group of cardiacs there was no patient with severe hypoproteinæmia. The average plasma volume was increased above normal, but there were no significant alterations in the total exchangeable albumin, in the fraction of total albumin found in the vascular compartment, or in the rate of albumin turnover. In the patients with proteinuria, the rate of metabolic degradation of albumin was abnormally low.

The present paper reports four cases in which hypoproteinæmia, accompanying congestive heart-failure, could be attributed to protein-losing gastroenteropathy. Three of them had chronic constrictive pericarditis. That the presence of congestive failure was pathogenetically related to the hypoproteinæmia in each case is shown by the correction of the metabolic defect when the cardiac lesion had been alleviated surgically.

Case-reports

Case 1.*—A white farmer was first admitted [N.I.H. 008262] in February, 1958, at the age of 23, for the investigation of œdema of over three years' duration. Except for the usual infectious diseases of childhood, he had been in good health until 1954, and he specifically denied having had tuberculosis, rheumatic fever, or any gastrointestinal disease. In 1954 he noted the gradual onset of œdema, periorbital at first, and then involving the ankles and legs. Shortly afterwards he had slight exertional dyspnœa. He was admitted to a local hospital for study, where laboratory tests revealed hypoproteinæmia. The clinical examination of the heart was unremarkable, except for "slight tachycardia". Blood-pressure was normal, as was a chest X-ray. The urine was devoid of protein, but contained a few casts. No clinical or chemical evidence of liver disease could be obtained. Because of the tentative diagnosis of hypoproteinæmia of unknown cause, he was treated with a high-protein, low-salt diet, and diuretics, with considerable relief of his œdema. His serum-protein levels fluctuated, at times rising almost to normal. In late 1957, however, his œdema became refractory, and increased so greatly in severity as to be incapacitating; and he was referred to the National Institutes of Health (N.I.H.) for further study.

He was a well-developed man in no distress. The salient features were pitting œdema of the lower legs, and venous engorgement in the neck, with pulse waves visible up to 4 cm. above the clavicles. The precordium was quiet, no point of greatest impulse could be felt, and percussion did not suggest cardiac enlargement. The blood-pressure was 120/80 mm. Hg, and the pulse-rate was 80 and regular. Venous pressure was 225 mm. saline. Routine blood-counts and urinalysis were normal. The serum-protein level was 3·1 g. per 100 ml., with 1·6 g. albumin. Serum-calcium was 8·2 mg. per 100 ml., and phosphorus was 4.3 mg. The following determinations and tests gave results within normal limits: blood-glucose and blood-urea, cholesterol, electrolytes, alkaline phosphatase, bilirubin, cephalin-flocculation test, thymol-turbidity test, and serological test for syphilis. Intradermal tuberculin tests were negative. The electrocardiogram showed low voltage of QRS complexes and T waves. X-ray examinations of the chest and heart showed that there was calcification of the pericardium in the region of the right ventricle, and that the pulsations of the heart and great vessels were abnormal. The cardiac contour was not abnormal in size or shape. Study of the gastrointestinal tract with barium showed slight coarsening of the mucosal pattern of the small bowel. Right and left heart catheterisations were performed, with the demonstration of moderate elevation of pulmonary arterial pressure, decrease in cardiac index, and pressure curves with contours compatible with the diagnosis of chronic constrictive pericarditis.

After a brief discharge, the patient returned for pericardiectomy. The clinical picture was unchanged, except that conservative treatment in the interim had reduced the œdema to some extent. Operation was performed through a bilateral anterior thoracotomy. The pericardium was thickened, as was the epicardium, but the two layers were not adherent. The

* For permission to report this case we are greatly indebted to Dr. Frederic C. Bartter, whose own investigations will be published subsequently.

area of calcification was found to involve pericardium which was adherent to the underlying diaphragm. The pericardium and parts of the epicardium were removed, the heart was thoroughly explored digitally, and myocardial biopsy specimens were taken. Histological examination of these tissues showed dense fibrosis and calcification of the pericardium, fibrous thickening of the epicardium, but no abnormality of the cardiac muscle.

After the immediate postoperative period, the patient noted considerable symptomatic improvement. Dyspnœa was no longer present, and his œdema cleared and did not recur, even after digoxin was discontinued and normal salt intake resumed. A definite upward trend in his serum-protein levels was evident by the second week after operation, and by late autumn of 1958, when he was readmitted for studies, the levels of total protein and albumin were 6·2 and 4·3 g. per 100 ml. respectively. Serum-protein values have been normal since that time.

Case 2.—This 2-year-old white boy was referred [N.I.H. 029801] in May, 1960, for study of œdema which had been present since the age of 14 months. He was the product of an uncomplicated full-term pregnancy; he weighed 7½ lb. at birth, and he grew and developed normally. Nutrition had been adequate. He had had no immunisations, and he had not contracted any significant infections. In June, 1959, his mother noted the onset of swelling about the eyes and ears, which gradually involved the entire body. His abdomen became protuberant, and his urine output was scanty. There were also several brief episodes of diarrhœa, with foamy foul-smelling stools, during the periods when œdema was at its worst. There was one episode of tetany in April, 1960, which responded quickly to treatment with calcium intravenously.

Between July, 1959, and April, 1960, he had several admissions to hospitals in his home State for diagnostic study. Hypoproteinæmia was found during the first of these admissions and was noted repeatedly during the year. Symptomatic treatment with salt restriction and diuretic drugs served to control the œdema partially. Because there was no evidence of hepatic or renal disease he was suspected of having the syndrome of "protein-losing gastroenteropathy", and he was referred to the N.I.H. for further study.

On admission he had considerable facial and generalised œdema, and he had a protuberant abdomen which was thought by some observers to give a fluid wave. The heart was unremarkable, and no murmurs were heard. The pulse-rate was 110 and regular. Œdema prevented a satisfactory auscultatory blood-pressure determination, but the systolic pressure, as determined by palpation, was 135 mm. Hg.

Diagnostic rests showed a normal urine, and the presence of a moderate hypochromic microcytic anæmia. A serum-iron of 37 μg. per 100 ml., with a normal total-iron-binding capacity, gave further evidence of iron deficiency. The serum-copper level was 139 μg. The white blood-cell count varied between 13,000 and 21,000, with up to 5% eosinophils. The sedimentation-rate was 35 mm. in the first hour (Westergren). Plasma proteins were low on repeated determinations; the initial values were albumin 1·5 g. per 100 ml. and total protein 3·7 g. X-ray examination of the gastrointestinal tract showed an abnormal pattern, particularly in the distal ileum, which was consistent with mucosal œdema, but which suggested the possibility of enteritis. After diuretic therapy this pattern reverted to normal. Chest X-ray revealed a normal-sized heart, but there was a smooth sharply delineated widening of the superior mediastinum. An angiogram showed occlusion of the superior vena cava. Venous pressures at this time were 290 mm. saline in the cephalic vein, and 210 in the femoral. The following determinations and tests yielded results within normal limits: blood-glucose and blood-urea, serum electrolytes, cholesterol, cephalin-flocculation test, serologic test for syphilis, quantitative fæcal-fat output, and prothrombin-time. Tuberculin tests were negative.

On the forty-sixth hospital day an exploratory thoracotomy was carried out. The pericardium was thickened, and milky-white. The upper mediastinum contained heavy œdematous areolar tissue and lymph-nodes, which were removed to give access to the superior vena cava. This vessel contained a firm thrombus, strongly adherent to the intima, and extending into tributary veins. As much of the clot as possible was removed through a longitudinal incision. The pericardium was then widely excised, and some thickened epicardial tissue was removed from the right ventricle. Bacteriological examination of the tissues removed did not disclose any pathogenic organisms. Microscopical examination of the material showed an organising thrombus of the superior vena cava, fibrous thickening of the pericardium without calcification, and dilatation and thickening of the walls of the lymph-spaces in the mediastinal nodes and perinodal tissues. Dilated lymph-spaces were also observed in the tissue of the pericardium itself.

The postoperative course was satisfactory. The remaining œdema continued to clear. The serum-albumin level, which had been raised above the initial value by infusions, became and remained normal. Venous pressure decreased more gradually; values of 210 mm. and 115 mm. saline were recorded in the jugular and femoral veins respectively, on the seventieth postoperative day. He was discharged in good condition in October, 1960, and was reported to be asymptomatic three months later. Serum-protein determinations shortly before discharge had shown an albumin level of 3·8 g. per 100 ml., and total proteins of 7·3 g.

Case 3.—This 17-year-old Negro boy was admitted for the first time [B.H. 325294] in August, 1959, with the story that for as long as he could remember he had tired easily, had been short of breath, and was unable to maintain the activity level of his peers. In 1957 he had noted ankle swelling on several occasions. Eight months before admission this had become constant, and had progressed to his mid-calf. There was no history of rheumatic fever, paroxysmal nocturnal dyspnœa, orthopnœa, hæmoptysis, or cough; and no family history of heart-disease was elicited.

He was thin and underdeveloped for his age. He looked chronically but not acutely ill, and he could lie flat in bed without distress. The left border of cardiac dullness was 13 cm. from the midline, and there was a large diffuse point of maximal impulse in the sixth intercostal space. The blood-pressure was 90/60 mm. Hg. The rhythm was that of atrial fibrillation, with an apical rate of 100, and a radial pulse-rate of 60. A grade-II systolic thrill could be palpated over the entire precordium. There was a split first sound in the mitral area, and a coarse, grade-IV systolic murmur heard best in the third left intercostal space. The neck veins were noticeably distended with the patient semirecumbent in bed, but not when he was erect. There was pitting œdema up to the knees, and the liver was palpable 2 cm. below the costal margin.

Venous pressure was 255 mm. saline; circulation time was 22 seconds (arm to tongue). The electrocardiogram showed atrial fibrillation, ventricular premature contractions, right bundle-branch block, and questionable right-ventricular hypertrophy. Generalised cardiomegaly and pulmonary vascular congestion were evident on the chest X-ray. Right-heart catheterisation was performed, and an increase in oxygen saturation was noted in the right atrium and ventricle. The right-atrial pressure was 10/5 mm. Hg. The catheter could be passed through an interatrial septal defect into the left atrium. The serum-albumin ranged from 2·2 to 2·5 g. per 100 ml., and the serum-globulins were 1·4 g. and 1·5 g. per 100 ml. on two occasions. All other laboratory data, including liver-function tests and a quantitative twenty-four-hour urinary protein determination, were normal.

At cardiotomy a large interatrial septal defect was found and corrected by invagination of the atrial wall. He had a stormy postoperative course, with recurrent massive bilateral pleural effusions, necessitating frequent thoracenteses. In addition to the usual measures, he was given 200 g. salt-poor albumin during his fourth postoperative week. After this, he improved considerably, and the remainder of his convalescence was uneventful. By the eighth postoperative week, his serum-albumin had risen to 3·8 g. per 100 ml., and the globulin level was 3·2 g. per 100 ml.

He was last examined in January, 1961, at which time he was a full-time student in high school. His only complaint was mild exertional dyspnœa. His heart was still enlarged, and there was a soft systolic murmur. The pulse was regular, the lungs were clear, and there was no œdema. The liver was still palpable 2 cm. below the costal margin. Liver-function tests and urinalysis were normal; and the serum-albumin and total protein levels were 4·4 and 8·1 g. per 100 ml. respectively.

Case 4.—This 56-year-old white man was admitted [P.H. 1308151] in April, 1959, for the treatment of recently progressive dependent œdema, of several years' duration. He had been under care at the Presbyterian Hospital since January, 1957, when he was treated for a bleeding duodenal ulcer. Twice previously, in 1935 and 1945, he had undergone plication of a perforated peptic ulcer. An episode of squeezing chest pain and shortness of breath in 1954, diagnosed as a myocardial infarction, had been treated with several weeks' rest in bed. After this he had felt well, except for mild but persistent ankle swelling and dyspnœa on exertion. On admission in 1957 he was noted to have elevated venous pressure in the arms, hepatosplenomegaly, and mild hypoalbuminæmia. Bromsulphalein retention was 35% after 30 minutes, with negative cephalin-flocculation and thymol-turbidity tests. The bleeding was controlled with medical treatment and the patient given a cardiotonic regimen to follow and discharged, to be readmitted six months later for an elective subtotal gastrectomy. A liver biopsy specimen taken at the time of operation was not considered diagnostic, but was thought compatible with cardiac cirrhosis, with some fibrosis present in the periportal areas. The heart was again noted to be of normal size and cardiac fluoroscopy was negative. After discharge his symptoms remained relatively stable, and he continued on his cardiac regimen. A bilateral stripping procedure for varicose veins was performed uneventfully. During the spring of 1959, however, ankle and leg œdema had progressed despite therapy, and he was readmitted.

At that time he had a blood-pressure of 105/75, with 10 mm. pulsus paradoxus. His neck veins were distended, though he was comfortable lying flat. The lungs were clear. The heart was not enlarged, and auscultation revealed quiet heart sounds and no murmurs. The liver and spleen were both palpable, there was severe pitting œdema bilaterally to the groin, and the venous pressure was 225 mm. saline. Urinalysis was unremarkable except for the finding of proteinuria+ which was absent on later analyses. Laboratory tests and estimations within normal limits included sedimentation-rate, blood-urea, phenolsulphonphthalein excretion, serum electrolytes, prothrombin-time, bilirubin, alkaline phosphatase, cholesterol, cephalin-flocculation test, and thymol-turbidity test. Two hours after a meal the blood-glucose was 138 mg. per 100 ml. The tuberculin test was positive at 1/1000. Chest X-rays showed probable old fibrotic apical tuberculosis with a heart of borderline-normal size and a straight right border. Cardiac fluoroscopy showed good pulsations on the left only. Right-sided cardiac catheterisation revealed right atrial and ventricular pressure curves with contours compatible with the diagnosis of contrictive pericarditis.

On a programme of bed rest, digitoxin, salt restriction, and diuretics, the patient had a good diuresis, with a weight-loss of 18 lb. On the thirty-fifth hospital day thoracotomy was performed, with the finding of thick constricting fibrotic tissue over the right-ventricular surface only. This was removed and, on microscopical examination, only chronic inflammatory changes and a few cholesterol deposits were noted. After operation the venous pressure immediately declined and by the eighth hospital day had fallen to 100 mm. saline. The post-operative course was uncomplicated except for a transient period of auricular fibrillation which responded to digitalis therapy. Two weeks after operation the serum-albumin level had risen from the value on admission of 2·0 g. per 100 ml. to 3·3 g. One month after operation the liver was no longer palpable, the firm spleen tip was still 1–2 cm. below the left costal margin, the patient had lost 14 lb. more weight and he was free of œdema.

TABLE I—^{131}I-ALBUMIN DATA IN TWO PATIENTS WITH CONSTRICTIVE PERICARDITIS

Patient	Serum-albumin (g. per 100 ml.)	Total exchangeable (g. per kg.)	Albumin half-time (days)	Albumin turnover (g. per kg. per day)	Plasma volume (ml. per kg.)
1 (before operation)	1·9	2·0	3·6	0·38	38
1 (after operation)	4·0	5·0	17·0	0·21	..
2 (before operation)	1·4	1·4	3·8	0·26	..
2 (after operation)	3·5	4·2	13	0·22	..
Normal	3·9	3·9	17±2	0·18±·03	40

Special Studies

Albumin turnover was measured in two of the subjects with ^{131}I-labelled human serum-albumin.† Plasma volume was determined in one patient by immediate isotope dilution; this was impossible in case 2 because of the extreme difficulty of satisfactory venepunctures. In each patient, with thyroidal uptake of ^{131}I blocked by the administration of stable iodine, the degradation of the labelled albumin was followed by measurement of the rate of urinary excretion of radioactivity. Plasma-protein levels were measured by paper-electrophoresis, and chemically by a modification of the method of Rutstein et al. (1954). From these data the total exchangeable albumin, half-time for albumin degradation, and absolute rate of albumin turnover could be calculated by the procedures of Berson et al. (1953). The results of these investigations, before and after operative intervention, are given in table I.

TABLE II—^{131}I-P.V.P.-EXCRETION STUDIES

Patient	No. days before or after operation	Albumin (g. per 100 ml.)	Total protein (g. per 100 ml.)	P.V.P. excreted in fæces (%)
1	−76	1·6	3·1	6·9
	−27	1·5	3·1	6·5
	+ 9	2·1	5·9	0·6
	+181	4·3	6·2	0·3
2	−44	1·5	3·7	5·3
	+12	3·5	7·0	0·2
3	− 9	2·2	3·7	9·2
	+41	3·8	7·0	1·5
4	−18	2·0	4·7	5·9
	+28	3·3	6·3	0·7

The preoperative turnover studies with ^{131}I-albumin, in the two patients in whom this procedure was carried out, indicate that hypoalbuminæmia was related to a subnormal body-albumin content. This, in turn, was the result of an exaggerated rate of albumin catabolsim, and not of a failure of albumin synthesis.

Abnormal gastrointestinal permeabilty to macromolecules was demonstrated in each patient by testing with ^{131}I-labelled polyvinylpyrrolidone (P.V.P.). The procedure was carried out as described elsewhere (Gordon 1959, Gordon, Bartter, and Waldmann 1959, Waldmann et al., in the press), and the results are recorded in table II. In every case, the preoperative result was clearly abnormal, and the change produced by surgical intervention was dramatic. The figures on case 2, since the test was carried out with P.V.P. of a lower molecular weight, are not precisely comparable with those obtained on the other three subjects, but the interpretation is the same (Gordon 1961). The serum-albumin values given in tables I and II do not agree exactly. Each subject had a

† RISA-M, obtained from Abbott Laboratories.

number of determinations; the values tabulated are those measured at as nearly as possible the same time as the radioisotopic investigations were made.

Discussion

In each of these four instances, a patient with congestive heart-failure manifested hypoproteinæmia, the mechanism of which could be shown to be the same as that found in the syndrome of "protein-losing gastroenteropathy". In the two patients studied with labelled albumin, it could be shown that the body albumin content was decreased, but that its fractional turnover rate was so elevated that the absolute rate of albumin production, in grammes per day, was in fact slightly increased. These figures rule out failure of albumin production, which one might expect with liver impairment or malnutrition, as the cause of the hypoalbuminæmia, and shift the blame to the excessive rate of albumin loss. The results of the studies with labelled P.V.P. implicate the gastrointestinal tract. None of these patients showed evidence of any of the primary gastrointestinal diseases that have previously been demonstrated to be accompanied by internal protein loss, and the restoration of the plasma-protein levels to normal after cardiac surgery makes it clear that there was no independent lesion of the gut.

By what means, then, could congestive failure dispose an otherwise normal gastrointestinal system to loss of plasma proteins? An obvious hypothesis is that the elevation of venous pressure led to excessive filtration of fluid from the capillaries and local œdema of the bowel wall, and that this in some way caused the outpouring of proteins. Elevation of venous pressure within the digestive system occurs in portal cirrhosis, and in the more advanced cases there is hypoalbuminæmia as well. These factors might be expected to cause œdema of the intestinal wall, which has, indeed, been reported (Pollak and Gerber 1943). Though the number of cases examined is not great, attempts to demonstrate the syndrome of protein-losing gastroenteropathy in cirrhosis have so far not been successful. Confirmation of this negative result is needed, but it appears that one may tentatively discard the idea that elevation of venous pressure within the gut is a potential cause of protein-losing gastroenteropathy.

An alternative hypothesis may be based on a consideration of findings in those patients with protein loss due to intestinal disorders, on the one hand, and of experiments reported by Blalock et al. (1936) on the other. The patients with so-called "idiopathic hypoproteinæmia" who have recently been shown to be suffering from the syndrome of protein-losing gastroenteropathy have manifested, in many cases, evidence of a disorder of the lymphatic system, particularly the lymphatics of the intestine itself (Gordon et al. 1959, Waldmann et al., in the press). Dilatation of the lacteals in the small bowel and stasis of their contents were demonstrated in twelve patients, in four of whom it was possible to study mesenteric lymphatics and lymph-nodes, which were also abnormal. Four patients had chylous effusions in the abdomen or chest, and three had evidence of localised lymphœdema of one or more extremities. It seems important, therefore, to search for evidence of some disturbance of the lymphatics in the present series of patients with heart-disease. That such a lesion of the lymphatic system might be present is suggested by clinical data in only one of these subjects—the boy whose pericardial tissue contained abnormally dilated lymph-spaces. The experiments reported by Blalock et al. (1936), however, indicate that a relation may exist between elevation of hydrostatic pressure in the venous system and dilatation and stasis in the lymphatics of the gastrointestinal system. They were able to produce these lesions of the lymphatics by total occlusion of the superior vena cava in the dog, thus obstructing outflow from both right and left thoracic ducts.

One of the patients discussed here had a thrombotic occlusion of the superior vena cava, and was in this respect comparable to the experimental animals mentioned. The others had a cardiac lesion which gave rise to a considerable elevation of venous pressure throughout the body, but the action of venous back-pressure in obstructing lymphatic outflow may well have given rise to the enteric protein loss. Clearly, the information available from the study of these cases does not permit a complete answer to the question of pathogenesis, and further experimental work will be necessary.

Recognition of the association of protein-losing gastroenteropathy with cardiac disease is of more than theoretical importance. Since many cases of congestive heart-failure and superior vena caval obstruction are susceptible to treatment, these conditions must be sought in the clinical study of a patient with hypoproteinæmic œdema of obscure origin. It is also to be hoped that, where facilities for special studies are available, it will be possible in the future to resolve some of the questions concerning the intestinal pathological changes in cases of this type. In addition, the possibility that a patient in cardiac failure may be losing plasma proteins into the gut must be borne in mind when one is evaluating the results of tests of liver function. Hypoproteinæmia in such patients should not be attributed to cardiac fibrosis unless there are other, independent signs of hepatic dysfunction, and the presence of protein-losing gastroenteropathy has been ruled out.

Summary

Four patients had congestive heart-failure, complicated by severe hypoproteinæmia. Three of them had chronic constrictive pericarditis, while the remaining one had a congenital atrial septal defect. The plasma-protein deficiency was demonstrated to be due to intraenteric loss, as in the recently recognised syndrome of protein-losing gastroenteropathy. There was, however, no primary disease of the gastrointestinal tract, and surgical treatment of the cardiac condition corrected the disturbance of protein metabolism in each case.

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SNAIL HÆMOLYMPH
AN AID TO SURVIVAL IN THE DESERT

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WITHOUT water, survival time in the desert has been estimated (Adolph 1947) at about four days when the maximum daily shade temperature is 40°C (104°F). All who cross the desert, whether on land or in the air, should know where and how to look for natural sources of water. Such instruction is given as a routine to R.A.F. aircrew flying over the desert and may be found in the Air Ministry pamphlet (1952) on desert survival that is included in survival packs. In practice, however, there may be no water to be found, particularly during the desert summer.

One of the instructors on the Middle East Air Force desert survival course at R.A.F. El Adem, near Tobruk, recently asked me whether the millions of white snails which are found in the desert in parts of Northern Libya might be valuable as a source of water. One of his pupils had noticed that fluid in some quantity escaped from the snails when the shell was smashed. The work described here attempts to answer the question, and was carried out in five stages:

(1) Identification of the snails.
(2) Analysis of the fluid obtained from them.
(3) Examination of the snails for organisms pathogenic to man.
(4) Giving the fluid to rats as their only source of water.
(5) Simulation of survival in the desert by a subject in a hot chamber, with the snail fluid as his only source of water.

Design of Experiments

Identification

The snails were all identified as *Eremina ehrenbergi* Roth. The shell is usually white and about 3 cm. in

Fig. 1—Specimen of snail, *Eremina ehrenbergi* Roth.

diameter (fig. 1). The genus Eremina is fairly widely distributed on the Northern fringes of the Sahara desert and extends eastwards into the Negev (Biggs 1959), though the population density and more precise location of the snails within this vast area are uncertain. Recent observation by the R.A.F. Regiment in Northern Libya suggests that the snails are few in areas where there is no desert scrub, and that they are plentiful only in Northern Cyrenaica. Where there is scrub, however, snails may be found in great numbers, both on rocks and on the dead bushes (fig. 2), where they usually æstivate in the dry season. In this state the snail retires into its shell and secretes across the opening a tough transparent membrane which must be almost impermeable to water vapour. The snail will remain in this condition, if necessary for years, until water is again available. During the summer in Northern Libya water is obtained fairly often by the snail from the early morning dew. The food of the snails is thought to be primarily lichens.

Analysis of the Fluid

Some of the snails were smashed in a mortar; and each snail yielded on an average 2·0 ml. of almost clear yellow-grey fluid, mixed with broken pieces of shell, slime, and

Fig. 2—Snails on dead bush in the Libyan desert.

debris. The fluid proved to be hæmolymph. (The snail has an open circulation consisting of a heart and primitive arterial system, but no veins: the hæmolymph returns to the heart in a simple sac known as a hæmocœle.) A preliminary analysis of the fluid showed:

Na^+ ..	50 mEq. per litre	pH	7·4
K^+ ..	10 mEq. per litre	Protein	3·8 g. per 100 ml.
Cl^- ..	30 mEq. per litre	Urea, Uric acid ..	Trace only

The freezing-point of the hæmolymph was depressed to −0·45°C, indicating a total osmolal concentration of 242 mM per kg. hæmolymph water, and hence an osmolarity of about 220 mM per litre hæmolymph. If sodium and potassium were the major cations present, then the osmolarity could not be much more than 120 mM per litre. In view of this discrepancy, the fluid was analysed for a large number of cations. This was done spectrographically at the Chester Beatty Research Institute. The results for the more important cations are shown in table I.

The total osmolar contents of cations is now a minimum of about 90 mM per litre. Since the first analysis showed that the concentration of chloride was only 30 mEq. per litre, and phosphorus in the spectrographic analysis was less than 1 mEq. per litre, there is clearly a considerable anionic deficit, though part of this would probably be made up by the hæmolymph protein. If the remaining anions were monovalent, then the total osmolarity of the solution might be in the region of 200 mM per litre, which is nearer the estimate made from the freezing-point depression.

Though the analysis was not complete, the figures looked promising. Simple comparison of the osmolarity of human urine at its maximum concentration of 1000 mM per litre and snail hæmolymph with a concentration of about 200 mM per litre suggests that most of the hæmolymph water should be available to the body. Indeed, since most of the water lost in desert climates is in the form of sweat, and salt loss is obligatory in sweat, the entire electrolyte content of the hæmolymph with the exception of magnesium might well be lost in the sweat,

TABLE I—QUANTITATIVE SPECTROGRAPHIC ANALYSIS OF IMPORTANT CATIONS IN SNAIL HÆMOLYMPH

Cation	mEq. per litre	mM per litre	Cation	mEq. per litre	mM per litre
Na^+	60·0	60·0	Ca^{++}	7·0	3·5
K^+	8·7	8·7	Mg^{++}	35·0	17·5

and hence constitute little osmotic load on the kidney. This would imply that nearly all the hæmolymph water would be available to the body. A further encouraging factor was the presence of protein in quantities which would contribute valuable calories.

The comparatively high concentration of magnesium was thought unlikely to have been an artefact caused by the inclusion of powdered shell in the ash used for spectrographic analysis, because the ash was prepared from a supernatant liquid obtained by centrifuging the hæmolymph at 2000 r.p.m. for 60 min.

The amount of hæmolymph required for survival would contain 1–2 g. of magnesium per day. This quantity was thought acceptable in view of the experiments of Anstall et al. (1959), who administered 1 g. magnesium per day (combined with 50 g. of peptone to give maximum absorption) to ten experimental subjects without ill effect.

The fluid to be investigated was obtained by smashing the shell. Pure hæmolymph is undoubtedly the major constituent of this fluid but the pure hæmolymph is certainly admixed with small amounts of fluid from other organs, and " hæmolymph " in this paper denotes what is in fact contaminated hæmolymph.

Examination for Pathogenic Organisms

The desert snail was thought unlikely to be a carrier of organisms pathogenic to man, since the human population of desert regions is small. For experimental simulation of survival conditions, the absence of pathogens had to be established. A few snails, therefore, were examined at the Wellcome Laboratories of Tropical Medicine. No protozoa, helminths, or bacteria known to be pathogenic to man were found, though a number of unidentifiable bacteria, some of which were fluorescent, were isolated from the various organs of the snail.

Animal Experiments

Snail hæmolymph was fed to rats to discover whether the fluid contained any toxins harmful to mammals, and to determine whether acute fluid loss from diarrhœa or vomiting would result from the action of any such toxins on the mammalian gastrointestinal tract.

A thousand live snails were, therefore, flown to this country from Northern Libya. They were washed to remove the worst of the sand and excreta adhering to the outside of the shells, and were then smashed on a wooden board with a blunt instrument. The board rested in a collecting bowl with a layer of parachute fabric between the two to act as a filter for macroscopic debris. A blow sufficient to smash the shell invariably ruptured the hæmocœle and clear fluid spilled out on the board. By the time this fluid has drained through the debris, however, it had acquired a certain amount of particulate matter, a brown colour, and an unpleasant and fishlike smell. The thousand snails yielded 2 litres of hæmolymph. Some of the water used for washing the snails was absorbed by them, but the soft part of the snail at the time of smashing was, on average, level with the opening in the shell. This was considered a fair degree of hydration and corresponded with the state of the dozen snails used for the initial analyses at the time when they were collected in the desert.

After collection, the fluid was frozen and portions were thawed daily for administration to two male albino rats (closely inbred experimental strain). The hæmolymph was the only source of fluid available to the animals, which were given a normal solid diet. The rats drank the hæmolymph with apparent unconcern and gained weight somewhat faster than expected over a period of twenty-four days, after which the hæmolymph was replaced by water. The animals at no time exhibited any gastrointestinal or other disturbances, and have remained well since.

Simulation of Survival in the Desert

The total daily water loss of a man resting in the shade in the desert varies from about 1·5 litres in the cool season to about 5 litres under the worst summer conditions. It was decided to aim between these extremes and simulate an environment of moderate severity, and to produce a daily water loss of some 3 litres, most of which would be sweat. In the average desert, water losses of this amount are produced by mean daily air temperatures of about 32°C (89°F) with maxima of 40°C (104°F), provided the subject is resting in the shade (Adolph 1947). For such a subject, daily sweat loss is a function of ambient temperature and the time of exposure. In the desert itself the time during which sweating may be taking place could be as much as twelve hours. For convenience this time was shortened in the laboratory to six hours and the ambient temperature was raised to a higher level so that sweat loss remained at the required figure. The subject was, therefore, exposed to the following environmental conditions in a hot chamber in the climatic research laboratory at the Institute of Aviation Medicine:

Dry-bulb shade air temperature	47·5°C (117·5°F)
Wet-bulb shade air temperature	29·2°C (84·6°F)
Humidity	21 mm. Hg
Wind speed	3 m.p.h.
Solar radiation	Nil

Wall temperature was equal to air temperature.

In practice, aircrew might have to fly over desert terrain after taking off from a base in a cool climate. The subject was, therefore, not acclimatised to heat before the experiment. He wore an R.A.F. tropical flying overall Mark 2 and remained in the chamber for six hours each day. He was weighed nude before and after the six-hour period, and the volume of any urine produced was measured. During the remaining eighteen hours of each day the subject lived his normal daily life, except that he did not eat or drink.

In desert survival, water must be conserved by producing urine of maximum concentration and minimum volume. This is easily done by withholding water until mild dehydration occurs. A sensitive indicator of this state is thirst, and the intake of hæmolymph during the experiment was therefore regulated by the subject to a rate which maintained him in a constant state of moderate thirst. For this reason the intake of hæmolymph on the first day, when the subject was initially well hydrated, was less than on succeeding days.

Ten thousand live snails were flown from North Africa, were smashed in a similar way to the initial thousand, and the 20 litres of hæmolymph obtained was frozen. During the experiment the fluid was drunk in aliquots, each of about 250 ml., at

TABLE II—WATER-BALANCE AND ANALYSIS OF URINE PASSED AT THE END OF THE SIX-HOUR PERIOD OF HEAT EXPOSURE ON FOUR SUCCESSIVE DAYS

—	Control	Day 1	Day 2	Day 3	Day 4
Nude weight at 10 A.M. (kg.)	..	84·54	81·69	80·06	79·22
Hæmolymph drunk (ml.)	..	1450	2290	2670	2470
Urine volume in 24 hours (ml.)	..	500	580	720	610
Sweat loss + insensible loss during heat exposure (g.)	..	3070	2880	2520	2610
Urinary Constituents:					
Na^+ (mEq. per litre)	162	167	94	80	68
K^+ (mEq. per litre)	11·8	9·7	5·6	4·1	3·6
Cl^- (mEq. per litre)	286	286	145	74	64
pH	5·3	5·1	5·4	5·4	5·2
Total N (mg. per ml.)	14·7	13·1	20·0	20·0	15·7
Inorganic P (mEq. per litre)	136	92	68	127	201
NH_4^+ (mEq. per litre)	37	32	40	31	44
Total titratable organic acids (mEq. per litre)	55	52	53	29	26

a rate which maintained the subject in the required state of thirst. Sweat loss was calculated as the sum of weight loss and hæmolymph intake during the period of exposure to heat, less the volume of urine produced over the same period. There is a small error here due to insensible loss from skin and respiratory tract during the six-hour exposure.

Urine passed at the end of each six-hour exposure in the hot chamber was analysed for sodium, potassium, chloride, phosphate, and ammonium ions, and its pH and organic-acid content were determined. Total nitrogen was also estimated. The intention was to measure twenty-four hour totals for all these solutes but, owing to an unfortunate error, the overnight-urine samples were thrown away after their volumes had been measured. The figures, therefore, refer only to concentration at the end of the period of exposure to heat on each day.

The experiment was not planned for any particular length of time except that it was hoped to achieve the four-day estimated survival time for a survivor lost in the desert under similar climatic conditions.

No food or fluid other than hæmolymph was taken during the experiment.

Results

The experiment was continued for four days and the results are shown in table II.

Though the fluid was drunk without flavouring on the first day, a flavouring of lemon essence and saccharine had to be added for the remainder of the experiment to eliminate nausea. Clinically, the condition of the subject was no different at the end of the experiment from that of one who has been on a fairly severe diet. There was no ketosis.

There was a detectable loss of weight, a general feeling of weakness, and a mild irritability. Otherwise the subject was fit and well, and remained alert mentally throughout the experiment. Apart from some nausea on the first day there were no gastrointestinal disturbances: constipation was complete throughout, and there was no vomiting.

During the exposure to heat, the subject sat or lay for most of the time. Sometimes he walked about, and this exercise was sometimes sufficient to induce dizziness, breathlessness, and a rapid rise in pulse-rate. These symptoms were probably due to the combination of severe heat stress and dehydration, giving incipient acute circulatory insufficiency, together with some hypoglycæmia from dieting. A survivor in the desert would be better off because the intensity of the heat stress would be less. In fact, the symptoms disappeared soon after the subject emerged from the hot chamber.

Discussion

The results show that snail hæmolymph in quantity during survival in the desert would enable a man to remain reasonably fit and well for at least four days in an environment with a daily maximum air temperature of 40°C (104°F). He would probably remain fit and well for a great deal longer and also he could withstand hotter desert climates just as capably, provided extra hæmolymph could be found. There is, of course, no control experiment. The subject who took part in the survival experiment would certainly have been moribund or dead at the end of the four-day period if no hæmolymph had been available. All the water in the hæmolymph, except that needed to cover excretion of urea produced from the protein, was available to the body. Virtually no obligatory water excretion by the kidney was necessary to accompany the electrolytes ingested in the hæmolymph. In fact, urinary sodium, potassium, and chloride levels fell consistently and significantly to minimum levels, indicating that most of the hæmolymph electrolyte was lost in the sweat. Taking sodium concentration, such a result is perhaps to be expected since values both for hæmolymph and sweat will have been in the order of 50 mEq. per litre.

The average daily intake of protein during the experiment was 84 g. Though there will certainly have been small amounts of other combustible substances in the hæmolymph, their calorific value was probably small compared with the 378 calories available from the protein. Protein is not an ideal food in desert survival because of the obligatory water excretion necessary to remove urea. There is little doubt, however, that the calories it provided contributed materially to the prevention of ketosis, and in this sense effected an economy of urinary water (Gamble 1950). If true, this implies that the hæmolymph protein is made up mainly of glucogenic aminoacids.

The necessary flavouring of the hæmolymph on the second, third and fourth days of the experiment does not materially alter the value of the work because flavouring materials may be present in the survival pack; and, perhaps more important, a man who is dying of thirst will drink anything.

This investigation was aimed primarily at evaluating snail hæmolymph as a source of water to the human body. If water is available, hæmolymph is unnecessary. Under such circumstances, however, there is little doubt that snails of the genus Eremina provide a valuable source of food.

Captain Gwatkin-Williams, R.N., and his crew of ninety-eight were torpedoed off the Libyan coast in 1916, and imprisoned for five months by the Arabs. In his vivid account (Gwatkin-Williams 1919) of their struggle for existence on the most meagre of rations he describes the mass consumption of snails by his crew. The snails were identical with those used in this investigation. Unlimited water was available, and the snails were boiled in it. If water is not available, then it is probable that the whole snail would effectively provide less water to the body than would hæmolymph alone, because the ratio of solid to liquid would be greater in the whole snail. Most of the water in hæmolymph, however, is available to the body, and water-balance might still be well on the credit side even if whole snails were consumed in an attempt to prevent dehydration.

The experiment shows that there can be little doubt of the value of snail hæmolymph as a source of water in desert survival. The only qualification to this statement concerns the state of hydration of the snail.

The animal is capable of large changes in body volume. When dehydrated, the soft part may recede so far into the shell that it can no longer be seen, and when allowed unlimited water the snail may bulge out of the opening of its shell. The dozen or so snails originally collected at the start of this investigation were found in the early morning imbibing dew. Their level of hydration was such that the soft part just filled the shell. Subsequent batches of snails sent from North Africa arrived in a more dehydrated state and it was presumed that they had lost a certain amount of moisture in transit. During washing they were, therefore, allowed to absorb water until they had achieved the same state of hydration as the snails originally collected. Recently, a batch collected by men of No. 1 R.A.F. (Field) Squadron and smashed on the spot yielded on average less than a quarter of the volume of the hæmolymph per snail compared with those used at Farnborough. This raises many new problems, though a hæmolymph considerably more concentrated than that investigated so far would probably still be useful as a source of water to the body. Other unknowns are the average levels of hydration of snails at different times of day, in different seasons, and in different localities. More work is also required on logistic problems of snail collection.

Practically, snails are of value only in large numbers. Even then, the effort of collecting the snails is considerable and this activity would have to be confined to darkness and dawn. There is an advantage in this since the state of hydration of the snails will be greatest if dew is present. In the desert winter the number of snails required would

be much smaller, and their use might therefore be a more practical proposition.

Men desperate for water have resorted in the Californian desert to the ingestion of blood from animals they have caught (McGee 1906). Adolph (1947) stated that while such a practice may satisfy thirst, it furnishes no water beyond that required for the metabolism of the proteins contained in it. This statement is certainly untrue as regards snail hæmolymph, though Adolph was probably not referring to invertebrates. Even in the case of the more concentrated blood of higher animals, however, this statement deserves a thorough re-examination.

Summary

Snails of the genus Eremina provide the desert survivor with a valuable source of water, and of food if water is available from elsewhere.

I am grateful to the Director-General of Medical Services, Royal Air Force, for permission to submit this work for publication. I am also grateful to Dr. P. J. R. Phizackerley of the Biochemistry Department, Oxford University, for his initial assistance; to the Rev. H. E. J. Biggs for identifying the snails; to Dr. L. G. Goodwin of the Wellcome Laboratories of Tropical Medicine for excluding pathogens; to Dr. P. Smith for analysis of urine; to Mr. C. Day, of the Chester Beatty Research Institute, for spectrography of the hæmolymph; to Mrs. Margaret Smith (née Gwatkin-Williams) for the loan of a copy of *Prisoners of the Red Desert*; to Wing-Commander K. H. W. Bazarnik, A.F.C., and Squadron-Leader Philip Norris, flying-personnel medical officers, sometime at El Adem; to all those who have assisted in the transport and processing of snails; and, finally, to Squadron-Leader J. R. Spencer, commanding officer, No. 1 R.A.F. (Field) Squadron, R.A.F., El Adem, without whose assistance in collecting snails and conducting experiments in the desert this investigation could not have been undertaken.

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DICHLORPHENAMIDE IN CHRONIC RESPIRATORY FAILURE

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As yet no respiratory stimulant is of proven value in the treatment of the alveolar hypoventilation of chronic respiratory failure. Acetazolamide aroused interest a few years ago, but its value was limited by a tendency to produce a hyperchloræmic acidosis (Galdston 1955, Platts and Hanley 1956). Two recent studies have shown improvement in both symptoms and blood-gas tensions in chronic respiratory failure treated with dichlorphenamide. This substance is a carbonic-anhydrase inhibitor, differing from acetazolamide in promoting greater renal excretion of chloride (Thomson et al. 1958, Naimark et al. 1960). But these two studies were made on hospital inpatients, some of whom had recently had an acute exacerbation of their respiratory disease. The following trial was designed to see whether this effect could be shown in a group of outpatients with chronic alveolar hypoventilation, whose condition appeared to be static.

Dichlorphenamide is a dichlorinated benzene sulphonamide. Like carbonic-anhydrase inhibitors previously described, it is characterised by a sulphamyl group. Animal studies have not shown any serious toxic effects after 6 months' continuous administration, and it has been used for several years in the treatment of glaucoma (Gonzales-Jimenez and Leopold 1958).

TABLE I—EFFECT OF DRUG ON pCO_2

Case no.	Sex	Age (yr.)	F.E.V.$_1$ (litres)	Mixed venous pCO_2 (mm. Hg)		
				Control level	With dichlorphenamide	
					After 2 weeks	After 4 weeks
1	M	32	0·50	75	66	58•
2	M	45	0·57	84	78	76‡
3	M	68	0·57	55	44•	48
4	M	61	0·60	56	48	56
5	M	50	0·85	68	66	66
6	M	62	0·60	73	58•	73†
7	M	64	0·75	64	64	64
8	M	40	0·70	68	54•	62
9	F	57	0·35	64	47•	58†
10	F	58	0·45	59	52	44•
11	M	65	0·84	61	51•	52•‡
12	M	56	0·61	54	42•	46•
13	M	36	0·61	62	60	57
14	M	47	0·45	79	74	67•†
15	M	50	0·60	62	60	54
16	M	57	0·60	58	57	58
17	M	57	0·45	58	53	52
Mean	..	..	0·59	65	57	58

• = significant fall in pCO_2. † = discontinued treatment.
‡ = continued treatment at reduced dose.

The Trial

The trial was in a group of patients who would normally be diagnosed clinically as having " chronic bronchitis and emphysema ". But, because the presence and degree of emphysema is often hard to establish with certainty, we have simply accepted them as being patients with non-specific chronic lung disease causing airway obstruction. No patient with a significant degree of reversible airway obstruction was included. This group can be said to have irreversible generalised obstructive lung disease (Ciba Guest Symposium 1959).

The criterion of chronic alveolar hypoventilation for inclusion in the trial was a mixed venous carbon-dioxide tension (pCO_2) of 54 mm. Hg or more, as determined by the rebreathing method of Campbell and Howell (1960). These patients formed a minority of those attending the outpatient clinic with obstructive lung disease, and all had a forced expiratory volume in 1 second (F.E.V.$_1$) of less than 0·9 litres (table I). All the seventeen patients had chronic bronchitis; in addition case 11 had bronchiectasis and case 13 had kyphoscoliosis. All had been attending the outpatient clinic of Hammersmith Hospital for at least a year, and none had had an acute exacerbation of respiratory disease in the preceding 3 months. Nine patients had previously been in heart-failure, but they were free of all signs of failure at the beginning of the trial, and with one exception remained so throughout. All other treatment was continued unchanged, and those who were on diuretics continued to take them (cases 1, 9, 10, and 16). The trial was held between July and September, when we hoped that the patients would remain free of infective exacerbations.

Since the degree of spontaneous and seasonal variation in the mixed venous pCO_2 was not known, the study was designed as a double-blind crossover trial. After initial observation for at least 2 weeks the patients were grouped into nine pairs of similar age and pCO_2 level. One member of the final pair during a longer period of observation showed a fall of pCO_2 to within normal limits, and this case was therefore discarded. One of each pair was given dichlorphenamide for 4 weeks, while the other had a placebo. The allocation was decided at random by the chief pharmacist. The first treatment period was followed by 4 weeks without either drug or placebo; the patients were then given the alternative preparation for a final 4 weeks. The

dose of dichlorphenamide was in all cases 50 mg. q.d.s., and the tablets were taken after meals.

The patients were seen fortnightly. Each time they were asked about changes in general condition, dyspnœa, and cough, and these were recorded as unchanged, better, or worse. Specific inquiry was made for headache, nausea, vomiting, and epigastric pain. Other side-effects which were volunteered were noted. In an attempt to control the effects of exacerbations of airway obstruction, infection, or heart-failure, the following were recorded at each visit: appearance of the sputum, presence of œdema or tracheal wheeze, increase of the jugular venous pressure, the weight, and F.E.V.$_{1}$. On each attendance, after the patients had been seated at rest for at least 15 minutes, the mixed venous pCO_2 was determined by the rebreathing method. A mass spectrometer was used as a rapid CO_2 analyser for the second stage of the procedure to prove a satisfactory plateau. Although this is more difficult to obtain in patients with severe respiratory disease than in normal subjects, we found that in practice most patients gave a satisfactory plateau at the first attempt. Blood was taken from an arm vein, without stasis, for estimation of the total plasma-CO_2 content. In addition, at every second visit, the respiratory and cardiovascular systems were fully examined and blood was taken for estimation of plasma-electrolytes and urea.

Results

Dyspnœa.—Seven of the seventeen patients claimed to be much less dyspnœic while taking dichlorphenamide, but six made similar claims while on the placebo. In no case did dichlorphenamide increase the sensation of dyspnœa.

Cough, general condition, symptoms and signs.—No changes of significance were noted save for the one patient (case 14) who developed heart-failure during the last week of the trial while taking the placebo.

TABLE II—MEAN VALUES OF PLASMA-ELECTROLYTES AND UREA

—	Sodium (mEq. per l.)	Potassium (mEq. per l.)	TCO_2 (mM per l.)	Chloride (mEq. per l.)	Urea (mg. per 100 ml.)
Before treatment ..	137·7	4·33	36·2	92·6	32·6
After 4 weeks' dichlorphenamide	136·1	3·86	31·3	94·7	36·8

Mixed venous pCO_2.—For the group as a whole a significant fall (at the 0·01 level) was found during treatment with dichlorphenamide, both at 2 and at 4 weeks. The mean level of pCO_2 at 4 weeks did not differ significantly from the level at 2 weeks (see table I). The mixed venous pCO_2 did not change significantly during treatment with the placebo. From the repeat estimations made before the start of treatment it was possible to define the limits of spontaneous variation of two estimates of pCO_2 at an interval of 2 weeks; the 95% limits of the change lay between ± 15·6% of the original observation. The figure of course includes the effect of variables in the patients as well as in the method, and therefore it is rather worse than that from repeated observation on any one occasion. As judged by this index the pCO_2 fell significantly in nine of the seventeen patients. The extent of this fall showed no correlation with the initial level of the pCO_2.

Total CO_2 content of plasma (TCO_2).—A significant fall ($P=0·001$) was found with dichlorphenamide at both 2 and 4 weeks (table II).

Other plasma-electrolytes and urea.—During treatment with dichlorphenamide there was a small increase in plasma-chloride levels. Fourteen patients showed a fall in plasma-potassium, and this was significant in eight. The mean fall was 0·47 mEq. per litre, but in two patients there was a fall of more than 1·0 mEq. per litre after 4 weeks' treatment. The blood-urea rose significantly in seven patients, and in four the rise exceeded 10 mg. per 100 ml. There was a rapid return to normal on withdrawal.

F.E.V.$_{1}$.—No significant change was noted after 2 weeks on dichlorphenamide, but at 4 weeks there was a slight but significant increase over control levels (0·59 litres rising to 0·64 litres). One patient (case 10) showed a steady rise in F.E.V.$_{1}$ throughout the whole period of the trial; if she is excluded the change in F.E.V.$_{1}$ is no longer significant. From the duplicate observations of the F.E.V.$_{1}$ made before the start of treatment one can define the limits of spontaneous variation, as was done for pCO_2, the 95% limits of the change lying between ±24%. So wide a variation is not surprising because all the patients had severe ventilatory impairment which renders the estimation of the F.E.V.$_{1}$ less repeatable. There was no change in F.E.V.$_{1}$ during treatment with the placebo.

TABLE III—SIDE-EFFECTS

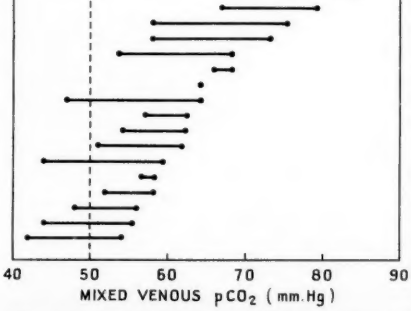
Side-effects	No. affected	Side-effects	No. affected
Headache	13	Limb paræsthesiæ	2
Anorexia	9	Sore calves ..	1
Nausea	4	Sore mouth ..	1
Ataxia	4	Blurred vision ..	1
Epigastric pain ..	3	Confusion ..	1
Vomiting	2		

Side-effects (table III).—The side-effects were severe. Only one patient did not complain of either headache or gastro-intestinal symptoms. In the majority the side-effects began in the first 3 days of treatment. Three patients had to abandon treatment (table I), two because of headache and gastro-intestinal upset, and the third because of headache and ataxia; two other patients had to reduce the dose. All side-effects improved a few days after treatment was stopped. Both headache and anorexia were worse in the patients with a significant response in the pCO_2.

Discussion

The results are similar to those previously reported in hospital inpatients. A significant reduction in pCO_2 was obtained in nine of the seventeen patients with chronic respiratory failure, and the extent of this reduction, which restored the pCO_2 to normal levels in five cases, suggests that it may be clinically useful (see figure). Other patients, however, showed no response to the drug in the dosage used. It does not seem possible to predict which patients will respond well; this is apparently unrelated to the initial level of the pCO_2, to the degree of ventilatory impairment, or to a previous history of heart-failure. How long dichlorphenamide can maintain improvement in man is not yet known, but a reduction in pCO_2 has persisted after 6 months in normal dogs (Merck Institute 1957).

The therapeutic value of dichlorphenamide remains to be established. Previous studies (Thomson et al. 1958, Naimark et al. 1960) have shown not only a fall in pCO_2 but also a rise in pO_2, and it is tempting to assume that such an improvement in blood-gas tensions must benefit the patient, particularly in view of evidence that the development of cor pulmonale is related to abnormalities of the blood-gas tensions. But Otis (1954) and Riley (1954) have suggested that when the work of breathing is greatly increased as in most of these patients, the raised pCO_2 may be a compensatory mechanism



The greatest fall in pCO_2 in individual patients. 50 mm. Hg is taken as the upper limit of normal.

enabling CO_2 excretion to be maintained with less ventilation. Consequently the oxygen consumed in respiratory work is reduced. In these circumstances they argue that no benefit will be gained from a simple increase in ventilation, despite return of the blood-gas tensions towards normal. Only if the increase in ventilation is achieved by reduction of the work of breathing will it be beneficial. It is not yet known whether dichlorphenamide affects the work of breathing; hence this potential objection to its use remains unanswered.

This trial was not designed to provide information about the mode of action of dichlorphenamide, which is still not known. Naimark et al. (1960) were unable to demonstrate a reduction in CO_2 production; the fall in pCO_2 must be mainly achieved by an increase in alveolar ventilation. If this was achieved by an increase in the overall minute ventilation one would expect that the patients would then be more dyspnœic unless there was a parallel increase in ventilatory capacity or reduction in the work of breathing. None of our patients were more dyspnœic; there was only a small increase in F.E.V.$_1$, the significance of which is doubtful, and several patients with much change in pCO_2 showed no change in F.E.V.$_1$. It would have been very difficult to obtain reliable figures for the minute ventilation of the outpatients in this trial and we did not attempt to do so. But the combination of a fall in pCO_2 and lack of change in F.E.V.$_1$ without exacerbation of dyspnœa suggest that dichlorphenamide cannot act solely by increasing the minute ventilation. The results are compatible with a reduction in the work of breathing. Loss of weight tended to be associated with a fall in pCO_2, but none of the patients was in heart-failure while on dichlorphenamide, and those with a history of heart-failure did not show a greater response. Part of the weight-loss may be due to anorexia, but even if it all represents diuresis it is unlikely that this would explain fully the effect on blood-gas tensions; in patients who responded to dichlorphenamide, a larger diuresis with only a small change in pCO_2 was induced by mersalyl or chlorothiazide.

In our series, in contrast to the previous studies with dichlorphenamide in respiratory failure, side-effects were frequent and troublesome, although we gave the same dose. The incidence in our hands was more like that reported in glaucoma (Gonzales-Jimenez and Leopold 1958). While it seems likely that alimentary symptoms may be a direct effect of the drug, headache may be related to changes in CO_2 tension in the tissues which may differ from that in the blood. Headache was most severe in those patients with the greatest fall in mixed venous pCO_2. The frequency of the side-effects suggests that they may greatly limit the effective clinical use of dichlorphenamide.

In view of the variable response and the frequency of side-effects we feel that dichlorphenamide should not be used indiscriminately, and our experience shows that the patients' subjective impressions can be misleading. Dichlorphenamide may be of value in treating CO_2 retention, but this should be shown to be present before treatment is started. Some indirect information can be gained from the F.E.V.$_1$ (which will usually be less than 1 litre before CO_2 is retained) and from an increase in the venous plasma-bicarbonate, but direct information should be obtained. The essential minimum is the measurement of the mixed venous pCO_2. This can be done quickly, simply, and reliably using the modified Haldane apparatus (Campbell 1960) and the rebreathing technique described by Campbell and Howell (1960). The measurement should be repeated to assess the effect of treatment. The dosage which we gave seems unsuitable for general application. The manufacturers now suggest that the dose should be gradually increased to 200 mg. per day over 1–2 weeks, and this may help to reduce the incidence of side-effects—though in our limited experience we have not found this to be so. The tablets should be taken after meals. We did not give any of our patients potassium supplements, but in view of the tendency of dichlorphenamide to lower the plasma-potassium level these will probably be required in some patients, particularly on long-term treatment.

Summary

A double-blind crossover trial of dichlorphenamide in seventeen outpatients with chronic respiratory failure is described; efforts were made to ensure that their condition was not fluctuating. In all but three patients the mixed venous carbon-dioxide tension fell, and the fall was significant in nine.

Other changes included a fall in venous plasma-carbon-dioxide content and potassium concentration, and a small loss of weight. There was a small rise in the forced expiratory volume in 1 second.

Side-effects appeared in all but one patient. Headache, nausea, anorexia, and epigastric discomfort were particularly troublesome. In three patients treatment was stopped because they were so severe.

We are indebted to Dr. C. M. Fletcher, Dr. J. G. Scadding, and Dr. Philip Hugh-Jones for permission to study their patients; to Dr. J. J. F. Merry, of Merck, Sharp & Dohme, Ltd., who supplied the dichlorphenamide and placebo tablets, and to Miss J. Allen, chief pharmacist, Hammersmith Hospital, who dispensed them; to Dr. R. M. Haslam, assistant lecturer in clinical chemistry, who did the biochemical estimations; and to Miss H. MacLeish and Miss E. Buchanan for technical assistance.

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THE ÆTIOLOGY OF RETROBULBAR NEURITIS IN ADDISONIAN PERNICIOUS ANÆMIA

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RETROBULBAR neuritis is a rare, though well-recognised complication of addisonian pernicious anæmia, and may be a presenting feature (Cohen 1936) or may arise during the course of the disease. Though there has been much discussion and controversy about the nature of this association (Turner 1940, Benham 1951, McAlpine and Goldsmith 1951, Hyland and Sharpe 1952, Hamilton et al. 1959), no satisfactory explanation has as yet been given

why only some patients with pernicious anæmia develop this condition. Before attempting to answer this question, the following known facts must be taken into account:

Sex Incidence

There is an overwhelming male preponderance of cases of retrobulbar neuritis in pernicious anæmia. Of 29 cases reported in the literature, 26 were males (Hamilton et al. 1959). Yet in pernicious anæmia and subacute combined degeneration of the cord males and females are equally affected.

Anæmia and Neurological Involvement

Turner noted that the development of amblyopia in patients with pernicious anæmia was not related to the duration of the disease, to the presence or degree of anæmia, or to neurological involvement. Full clinical and pathological details are not available in all the 31 cases of retrobulbar neuritis in pernicious anæmia under review; but in about one-quarter of the patients there was no anæmia, and in one-sixth of patients there was no evidence of subacute combined degeneration of the cord.

" Pre-pernicious-anæmia " State

Jewesbury (1954) showed that patients with a histamine-fast achlorhydria are, in varying degrees, liable to show manifestations of vitamin-B_{12} deficiency, but the relative susceptibility of the peripheral nerves, spinal cord, and bone-marrow is unpredictable. Retrobulbar neuritis may arise in the " pre-pernicious anæmia " state—in which there is achlorhydria with gastric atrophy, poor absorption of vitamin B_{12} corrected by intrinsic factor, and a low or low-normal serum-vitamin-B_{12} level without anæmia (Callender and Denborough 1957)—and such patients may later have pernicious anæmia (Cohen 1936, Leishman 1952, Nelson and Weaver 1956, Heaton, McCormick, and Freeman 1958).

The Additional Factor

This evidence suggests that there must be an additional factor responsible for the development of retrobulbar neuritis in pernicious anæmia and in the " pre-pernicious-anæmia " state which is far commoner in males than females, and which acting alone does not cause anæmia or subacute combined degeneration of the cord. We believe that smoking is this factor, the optic nerves being rendered unduly sensitive to the toxic effects of tobacco owing to vitamin-B_{12} deficiency. Evidence will now be presented in support of this hypothesis.

Tobacco Amblyopia and Pernicious Anæmia

Leishman (1952) indicated that tobacco amblyopia and pernicious anæmia coexist in the same subject more often than can be accounted for by pure chance. He found that 3 of his 15 cases of tobacco amblyopia also had pernicious anæmia, and a further 7 cases of pernicious anæmia were found among the records of 60 patients with tobacco amblyopia seen at the Tennant Institute and Kilmarnock Infirmary.

Unfortunately, the smoking habits of patients with retrobulbar neuritis of pernicious anæmia have not always been recorded. A review of the 31 published case-reports revealed that 15 patients were specifically reported as being smokers while the smoking habits of the remaining 16 were not recorded. In no instance, however, was it stated that the patient was a non-smoker.

McAlpine and Goldsmith (1951) wrote:

" The predilection for males shown by the retrobulbar neuritis of pernicious anæmia suggests that the condition cannot be explained solely in terms of a deficiency factor. At the present time the evidence pointing to tobacco as a contributory cause is slight but may increase as more observations on this point are made."

Benham (1951) and Hamilton et al. (1959) dismissed tobacco as a possible cause of amblyopia in their patients with pernicious anæmia on the grounds that only heavy smokers have amblyopia, and that the vision continued to deteriorate even when they stopped smoking. It is known, however, that $^1/_2$ oz. of tobacco a week or ten cigarettes a day are quite enough to produce tobacco amblyopia under certain conditions, such as malnutrition or excessive consumption of alcohol; and withdrawal of tobacco does not always result in the arrest of the amblyopia (Traquair 1930, Schepens 1946, Heaton 1960). Traquair found an average weekly consumption of 3 oz. in 1525 cases of tobacco amblyopia and that the mean age of these patients was 55. According to Edwards et al. (1959) the normal healthy pipe smoker, aged 60, smokes $2^3/_5$ oz. of tobacco a week; hence a patient with tobacco amblyopia smokes only a very little more than his healthy counterpart.

In an earlier paper (Heaton, McCormick, and Freeman 1958) we produced evidence that in persons with even mild vitamin-B_{12} deficiency the optic nerve is unduly sensitive to the toxic effects of tobacco. In 13 patients with tobacco amblyopia the serum-vitamin-B_{12} level was significantly lower than that of normal controls. Other clinical manifestations of vitamin-B_{12} deficiency may be absent because, in pipe smokers and heavy cigarette smokers, amblyopia may precede the onset of anæmia, glossitis, neurological involvement, or a megaloblastic bone-marrow, by months or even years. The effect of parenteral vitamin-B_{12} in improving the visual acuity and completely reversing the changes in the visual fields was most encouraging, even if the use of tobacco was continued.

Pipe smoking is much more liable to produce amblyopia than cigarette smoking. As many more men smoke pipes than women, and even cigarette smoking is commoner amongst men, this could account for the overwhelming male incidence of retrobulbar neuritis in pernicious anæmia.

If the hypothesis that tobacco is an essential factor in the ætiology of retrobulbar neuritis in pernicious anæmia is correct, then the visual-field changes should be the same as those found in tobacco amblyopia. The field changes in tobacco amblyopia are very characteristic. They consist of a centrocæcal scotoma, usually bilateral, though not necessarily equal on the two sides. The scotoma is horizontally oval, with a sloping edge, and most easily detected by a reduced stimulus such as a red, or small white, test object. The defect for colour exceeds that for white, and there are usually definite nuclei within the scotoma on the horizontal meridian. An impairment of the temporal colour-field exists within the 30° circle and, in the more advanced cases, a similar defect is also seen to a small test object.

Unfortunately, most of the fields reported in cases of retrobulbar neuritis in pernicious anæmia are incomplete. Some had only perimetry done and slight peripheral constriction of the field was found (Cohen 1936). With a gross reduction in the visual acuity, as in these cases, the central fields must have been involved by scotomata. In other cases there is little detail of the exact type of scotoma and coloured test objects were not used. The detailed examination of a scotoma is not always easy,

requiring as it does an intelligent patient, especially when the visual acuity is 6/60 or less, owing to difficulty in fixation.

Traquair (1942) published a field with a centrocæcal scotoma in a case of pernicious anæmia with retrobulbar neuritis. He gave no clinical details and no red object was used. Though incomplete, it could be a tobacco-amblyopia field. In the text he stated that the visual fields in pernicious anæmia do not present any distinguishing features and are similar to those of Leber's disease—with a dense scotoma freely involving the fixation area, possibly fibre-bundle defects, and frequent involvement of the peripheral field. The field he published does not, however, substantiate this statement.

Benham (1951) described 5 cases of optic atrophy in 112 patients with subacute combined degeneration of the cord and in 3 patients peripheral and central fields were charted and a red test object used. In 2 patients there was considerable concentric contraction of the peripheral fields. This is unusual in tobacco amblyopia, though it can occur (Carroll 1944). In the first case reported, the centrocæcal scotomata had steep edges and, though this is not typical of tobacco amblyopia, the reduction of the temporal field to 15/2000 is characteristic of this condition. In the second case, a very accurate field could not be obtained as the vision was reduced to 3/60 in each eye; but, when recovering, the fields became like that of tobacco amblyopia. The third case is absolutely typical of tobacco ambylopia, as Benham himself admits.

McAlpine and Goldsmith (1951) described a case of optic atrophy in pernicious anæmia with bilateral centrocæcal scotomata to small red, green, and blue test objects; this is typical, as far as it goes, of tobacco-amblyopia fields.

In retrobulbar neuritis of pernicious anæmia, the histological findings in the optic nerves (Bickel 1914) appear similar to those observed in tobacco amblyopia (Duke-Elder 1954). Areas of degeneration in both optic nerves, with considerable proliferation of the neuroglia and round-cell infiltration in the tissues and around the blood-vessels, have been described in both conditions. A comparison of the histological findings, however, is not as helpful as it might be, because only one published report on the pathological appearances of retrobulbar neuritis of pernicious anæmia could be found.

Case-reports

We present 2 cases of retrobulbar neuritis in addisonian pernicious anæmia.* The visual fields were investigated by only one experienced observer (Mr. A. J. A. McCormick) in order to ensure uniformity of technique. The serum-vitamin-B_{12} levels were estimated by microbiological assay with *Euglena gracilis* var. *bacillaris* as test organism (Mollin and Ross 1952, 1954).

THE FIRST CASE

A man, aged 62, was initially seen at the Bristol Eye Hospital in June, 1956, with a 3-month history of failing vision. He had been smoking 4 oz. of strong pipe-tobacco a week for over 35 years. His visual acuity was right 6/24, left 6/18. The ocular fundi were normal. The visual field on the right showed a small centrocæcal scotoma to 2/1000 white and a larger one to 10/1000 red; on the left there was gross depression of the temporal field to 15/1000 red only. Because the field changes were attributed to tobacco amblyopia, he was advised to stop smoking immediately and was given vitamin-B complex by mouth.

In March, 1957, he was admitted to hospital for further investigation. Evidently, he had not only failed to respond to the standard treatment of tobacco amblyopia but he now gave a 3-month history of soreness of the tongue, slurring of speech, and numbness and paræsthesiæ in both legs below the knees. The tongue was smooth and red at the edges. Both discs were very pale and his visual acuity had deteriorated to right 6/60, left 2/60. The fields, which were now difficult to chart accurately, showed on the right a large centrocæcal scotoma to 3/1000 white and on the left to 15/1000 white with gross depression of the temporal fields in both eyes to 15/1000 red. Examination of the other cranial nerves showed no abnormality. There was no weakness or wasting of the limbs, and apart from the ankle-jerks being diminished all the reflexes were normal. The plantar responses were flexor. There was impaired sensation to pinprick in both legs below the knees, and diminished position and vibration sense in the feet.

The hæmoglobin level was 86% (12·7 g. per 100 ml.), hæmatocrit value 40%, mean corpuscular hæmoglobin concentration 32%, and the peripheral blood-film was normocytic normochromic. A histamine-fast achlorhydria was present; and biopsy material from the sternal marrow was megaloblastic (Dr. F. G. Bolton). The serum-bilirubin level was 0·2 mg. per 100 ml. The serum-vitamin-B_{12} level was 15 μμg. per ml.

Parenteral administration of cyanocobalamin 100 μg. daily for 14 days, followed by 100 μg. twice a week, improved the vision dramatically. 2 months after the start of treatment the visual acuity was right 6/24, left 6/12, and the fields were now typical of tobacco amblyopia. On the right there were two small centrocæcal scotomata to 1/1000 white, instead of the larger one to 3/1000 white previously recorded, and gross depression of the temporal field to 15/000 red; on the left there was a centrocæcal scotoma (far smaller than before) to 15/1000 white, with two small cores to 1/1000 white. His vision further improved to 6/12 in both eyes in 3 months and to 6/9 in 6 months, and the fields by then had almost returned to normal.

It seems reasonable to suggest that in this patient the onset of visual failure and the typical changes in the visual fields of tobacco amblyopia can be regarded as an early clinical manifestation of vitamin-B_{12} deficiency. It is of particular interest that in this case of pernicious anæmia the deterioration of vision and the defect in the visual fields preceded the onset of anæmia, glossitis, and signs of peripheral neuropathy and sensory ataxia by more than 9 months. We suggest that the retrobulbar neuritis was due to the optic nerves being rendered unduly sensitive to the toxic effects of tobacco owing to vitamin-B_{12} deficiency.

THE SECOND CASE

A man, aged 75, was admitted to hospital in June, 1956, under the care of Dr. J. A. Birrell with a 6-week history of anorexia, weakness, swelling of the ankles, and loss of weight. He was wasted and very pale; and glossitis and peripheral œdema were present. The hæmoglobin level was 33% (4.4 g. per 100 ml.) red-cell count 1·22 million per c.mm., colour index 1·36, mean corpuscular volume 121 c.μ, reticulocytes less than 1%, and white cells 1450 per c.mm. (lymphocytes 81%, neutrophils 16%). The serum-bilirubin level was 0·7 mg. per 100 ml. There was a histamine-fast achlorhydria and the bone-marrow was megaloblastic. He was treated with 'Anahæmin' 2 ml. daily, and on discharge his hæmoglobin had risen to 70%.

In February, 1958, he attended the Bristol Eye Hospital with a 4-month history of failing vision. He had started smoking a pipe—2 oz. of tobacco a week—16 months previously. His visual acuity was 6/60 in each eye and the optic discs were pale. He had classical tobacco-amblyopia fields; there were centrocæcal scotomata to 15/1000 red with two cores to 3/1000 white in both eyes. No other abnormal physical signs were detected, and there was no evidence of peripheral neuropathy or spinal cord involvement.

For the last 18 months he had been treated with anahæmin 2 ml. twice weekly. His hæmoglobin level was now 93% (13·8 g. per 100 ml.), and examination of the peripheral blood was normal. The serum-vitamin-B_{12} level was 130 μμg. per

* Reference was made to these cases in an earlier paper. (*Lancet*, 1958, ii, 286.)

ml. He was given parenteral cyanocobalamin 100 μg. twice a week and allowed to continue smoking. Within two months his vision had improved to right 6/12, left 6/9; and his fields had almost returned to normal.

It is of particular importance that this man with pernicious anæmia had no amblyopia when he was very anæmic, with a hæmoglobin level of 33%, and that at that time he was a non-smoker. When we first saw him, some 20 months after treatment with anahæmin, his hæmoglobin had risen to 93%, though the level of vitamin-B_{12} in the serum was low at 130 μμg. per ml. It is evident, however, that this degree of vitamin-B_{12} deficiency was not sufficient to produce anæmia or signs of peripheral neuropathy or spinal cord involvement, though it was quite severe enough to cause retrobulbar neuritis in this patient within 12 months of his starting smoking.

In this case, as in the first, the retrobulbar neuritis can reasonably be attributed to a combination of two essential factors—namely, vitamin-B_{12} deficiency which, in turn, rendered the optic nerves sensitive to the toxic effects of tobacco. This hypothesis is supported by the fact that we allowed this man to continue smoking as heavily as before, and after 2 months' treatment with cyanocobalamin his visual acuity and visual fields had almost returned to normal.

Conclusions and Summary

We consider that the ætiology of retrobulbar neuritis in addisonian pernicious anæmia cannot be satisfactorily explained on the basis of a deficiency factor alone, because:

1. There is an overwhelming male preponderance of cases. Of 31 patients reviewed, 28 were males, whereas in pernicious anæmia and subacute combined degeneration of the cord the sexes are equally affected.
2. Retrobulbar neuritis in pernicious anæmia is not related to the duration of the disease, or to the degree of anæmia, and may occur independently of anæmia and signs of peripheral neuropathy, myelopathy, or encephalopathy.
3. In all the published cases reviewed, not a single patient is reported as being a non-smoker.

We believe that the additional factor required is smoking. We have presented evidence that tobacco amblyopia and retrobulbar neuritis in pernicious anæmia are one and the same condition, and that retrobulbar neuritis in pernicious anæmia and in the " pre-pernicious-anæmia " state is due to the optic nerve being rendered sensitive to the toxic effects of tobacco owing to vitamin-B_{12} deficiency.

We thank the consultant staff of the Bristol Eye Hospital for permission to study and treat their patients; Mr. A. J. A. McCormick for charting the visual fields; and Miss A. Sinclair Rose for the microbiological assays.

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INTRATHORACIC PRESSURE DURING INTERMITTENT POSITIVE-PRESSURE RESPIRATION

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ARTIFICIAL respiration by intermittent positive pressure has been used in anæsthesia for at least two decades (Guedel 1940), and is now coming into favour as a means of emergency resuscitation in mouth-to-mouth breathing. In these applications it is required only for short periods. As a long-term measure it was introduced by Lassen (1953) in the treatment of acute anterior poliomyelitis, and has proved lifesaving not only in this condition, but also in other diseases such as polyneuritis, barbiturate poisoning, tetanus, myasthenia gravis, and chronic pulmonary disease.

The effect on the circulation of intermittent positive-pressure respiration (I.P.P.R.) and also of artificial respiration in a tank respirator (Beck et al. 1952) can be compared to a series of minor Valsalva manœuvres: each inspiration causes a rise of intrathoracic pressure relative to the pressure on the body surface. This impedes venous return to the heart, because flow into the right heart falls as the intrathoracic pressure rises (Brecher and Mixter 1953). This effect is not serious in a patient in good general condition, but is thought important in one who is severely ill (Maloney et al. 1953)—a view which has led to the development of respirators which can provide subatmospheric pressure in the trachea during expiration. This view is supported by investigations on animals (Rost 1932, Hubay et al. 1954), but the obstruction to venous return has not been adequately determined in man, and this paper reports observations bearing on its extent using different types of mechanical respirators designed for clinical use.

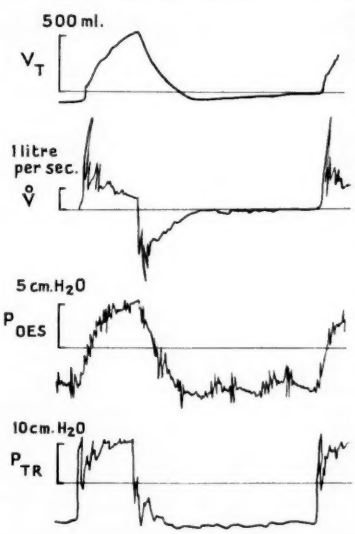

Fig. 1—The four measurements made with each respirator. In this example respirator 1B was used with subatmospheric pressure between inspirations.

Tidal volume (V_T), tracheal air-flow ($\dot{V}$), œsophageal pressure (P_{OES}), tracheal pressure (P_{TR}).

In artificial respiration there may be changes in the filling pressure between the right atrium and the right ventricle,

and the cardiac output may be altered. These, however, are secondary effects depending not only on the rise in intrathoracic pressure but also on the extent to which the circulation is able to adjust to it. The primary disturbance is the increase in intrathoracic pressure, and we have, therefore, taken changes in the mean intrathoracic pressure as the index of the change of pressure gradient which is produced by I.P.P.R. and which tends to obstruct the venous return.

The Investigations

Methods

Two patients, severely paralysed by poliomyelitis, were examined. Patient A was a man aged 31, patient B was a woman aged 34. Patient A had a vital capacity of about 500 ml. and was examined while asleep. Patient B had no spontaneous respiration. They were receiving I.P.P.R. through a right-angled tracheotomy tube (Spalding and Smith 1956), the cuff of which was inflated to provide an airtight seal with the trachea. All respirators were used at a rate as close to 16 respirations per minute as could be obtained.

9 respirators were examined, all but 1 (no. 9) being well-known commercially available machines. Their names are given in the appendix. With each respirator the tracheal and œsophageal pressures, the tracheal air-flow, and the tidal volume were measured by capacitance manometers and recorded on a 4-channel direct-writing pen oscillograph (Opie, Spalding, and Stott 1959). The intrathoracic pressure was measured in the œsophagus with a water-filled polyethylene tube, 0·5 mm. bore and 100 cm. long (Dornhorst and Leathart 1952).

The mean œsophageal pressure throughout the whole respiratory cycle was calculated from the records, and is expressed as rise above or fall below the resting level. The resting level is the œsophageal pressure when the paralysed patient is not receiving artificial respiration, and the chest is in the relaxed position.

Results

Fig. 1 is a typical record of the four measurements made, and in this instance the effect is shown of sub-atmospheric (" negative ") pressure in the trachea throughout the period between inspirations. Figs. 1 and 2 show the wave-form of the tracheal pressure provided by each respirator, together with simultaneous œsophageal-pressure records. As the air enters the chest the œsophageal pressure rises, and fig. 3 shows the relation of the tidal volume to the mean œsophageal pressure for the different respirators and the two patients.

2 of the respirators (nos. 2 and 3) were used on both patients in order to provide a standard of comparison. The values obtained on the two patients with the same respirator did not coincide, because the compliance of the chest wall was different, being 87 ml. per cm. H_2O for patient A, and 210 ml. per cm. H_2O for patient B. The results shown in fig. 3 were, therefore, adjusted to conform with the average compliance found in similar patients with respiratory paralysis—namely, 110 ml. per cm. H_2O (Opie et al. 1959)—by multiplying the mean œsophageal pressure by the factor:

$$\frac{\text{Patient's chest-wall compliance}}{\text{"Average patient's" chest-wall compliance.}}$$

After this correction to the results the two respirators had similar effects on the mean œsophageal pressure of both patients. Fig. 4 shows the results, corrected for chest-wall compliance, from the study of both patients and all the respirators.

The mean intrathoracic pressure was plotted against the mean tracheal

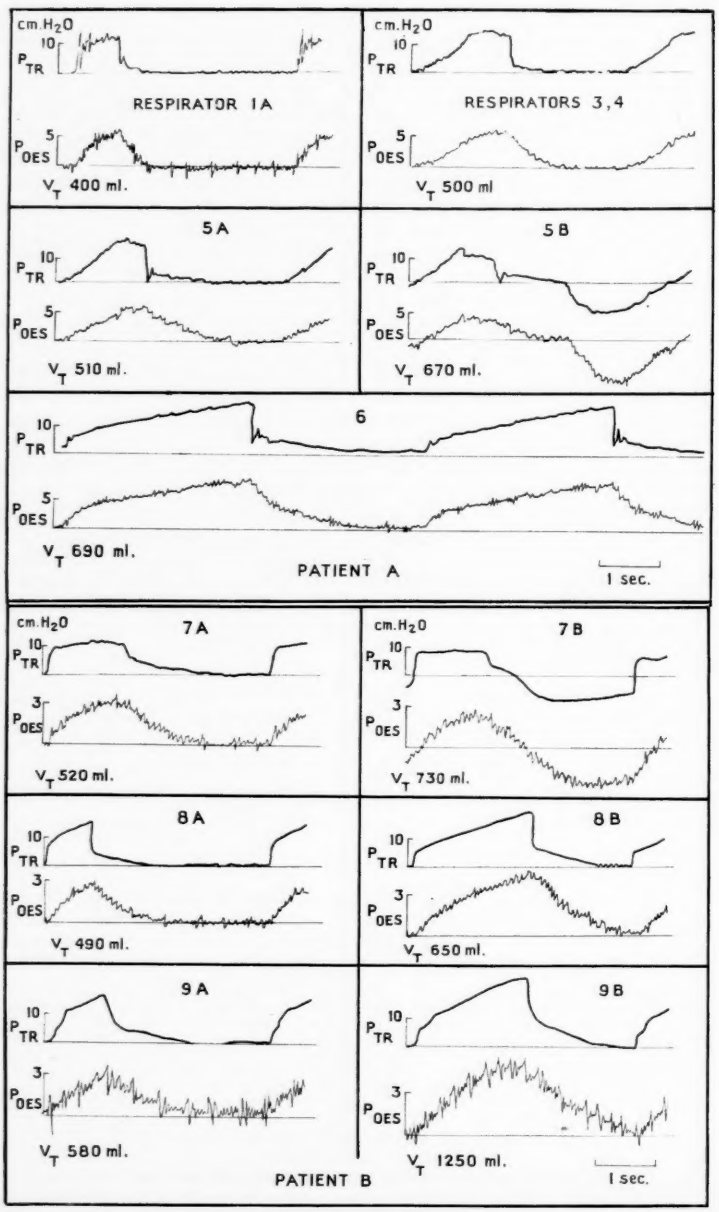

Fig. 2—The tracheal pressure (P_{TR}) and œsophageal pressure (P_{OES}) with each of the 9 respirators. Tidal volume (V_T) is given.

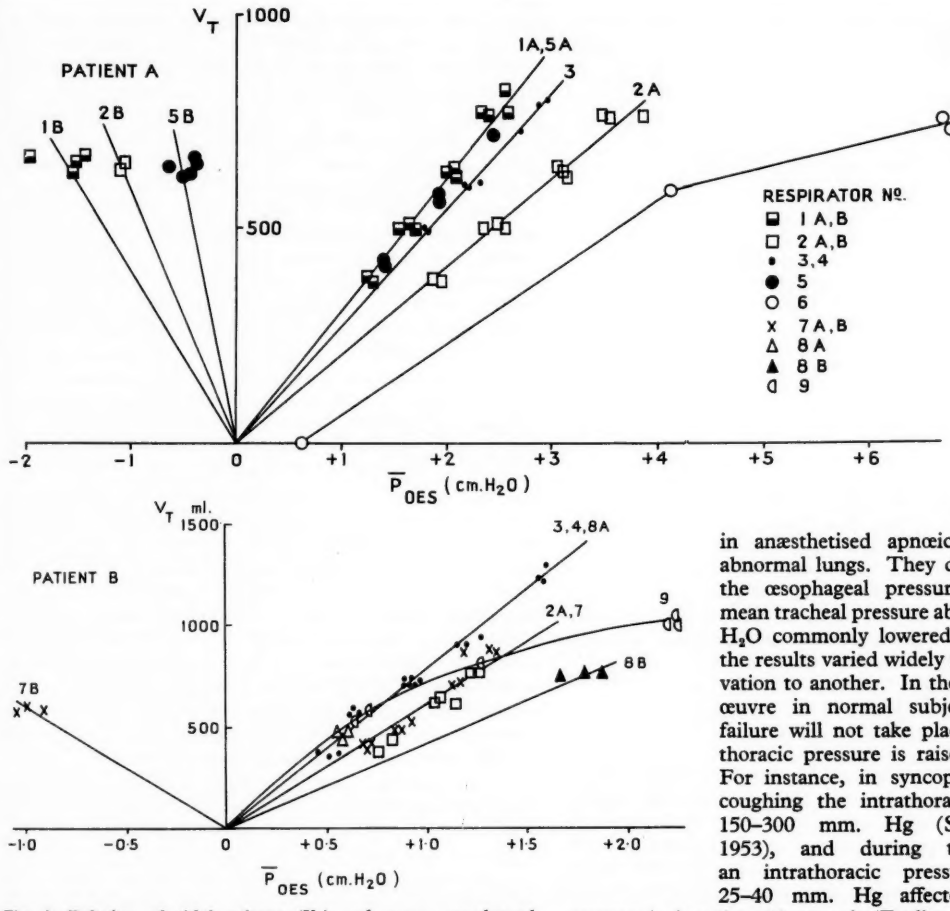

Fig. 3—Relation of tidal volume (V_T) and mean œsophageal pressure ($\overline{P}_{Oes}$) with different respirators in patients A and B.

pressure. The relation was linear within the limits examined, regardless of wave-form of the tracheal pressure, and of whether subatmospheric pressure was introduced (fig. 5).

Discussion

These observations show the pressure gradient to be overcome during I.P.P.R. if venous return and therefore cardiac output are to be maintained. A paralysed adult patient will often receive total ventilation of about 8 litres per minute at a frequency of 16 respirations per minute, and what takes place at this level of ventilation will be especially considered.

The mean intrathoracic pressure during I.P.P.R. at a given tidal volume and frequency varies from one respirator to another. At a tidal volume of 500 ml. and a frequency of 16 per minute in the patient with an "average" chest-wall compliance, the mean œsophageal pressure is raised 1·0 cm. H_2O (respirators 1, 5A) to 3·5 cm. H_2O (respirator 6) above the resting level (fig. 4). The assessment of the significance of this increase in thoracic pressure is important. Werkö (1947) found that during I.P.P.R. in spontaneously breathing subjects whose circulation was normal, mean tracheal pressures above about 7 cm. H_2O caused a fall in cardiac output. In the relaxed patient, a mean pressure of 7 cm. H_2O in the trachea implies a mean intrathoracic pressure nearly 3 cm. H_2O above the resting level (fig. 5); but Werkö's subjects were not paralysed, and in those instances where he measured œsophageal pressure he found that there was a very wide scatter due to varying muscular activity in the chest wall. Nealon et al. (1959) measured cardiac output at various mean tracheal pressures in anæsthetised apnœic patients with abnormal lungs. They did not measure the œsophageal pressure, and though mean tracheal pressure above about 8 cm. H_2O commonly lowered cardiac output the results varied widely from one observation to another. In the Valsalva manœuvre in normal subjects circulatory failure will not take place unless intrathoracic pressure is raised much more. For instance, in syncope produced by coughing the intrathoracic pressure is 150–300 mm. Hg (Sharpey-Schafer 1953), and during trumpet-playing an intrathoracic pressure of about 25–40 mm. Hg affected the blood-pressure in less than 10 seconds (Faulkner and Sharpey-Schafer 1959). The Valsalva manœuvre, however, is an acute experiment, whereas patients receiving I.P.P.R. do so for long periods, even for many years. Experiments conducted in connection with high-altitude flying, and involving raised intrathoracic pressure for periods up to some hours, have shown that when circulatory failure occurs it is accompanied first by pooling of blood in the

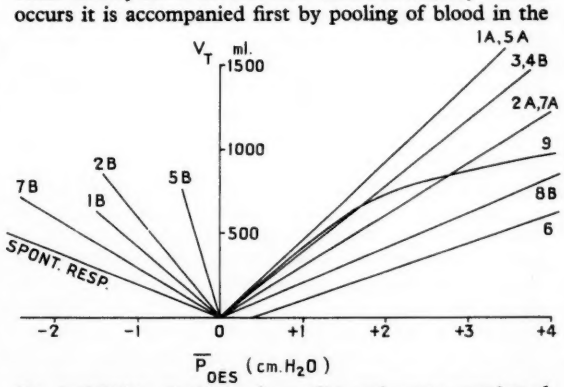

Fig. 4—Relation of tidal volume (V_T) and mean œsophageal pressure ($\overline{P}_{Oes}$) with all respirators, chest-wall compliance being adjusted to that of the "average" patient.

Individual points are too numerous to show clearly, but can be calculated from fig. 3. The line for spontaneous respiration is based on observations on normal supine subjects (Opie, Spalding, and Stott 1959).

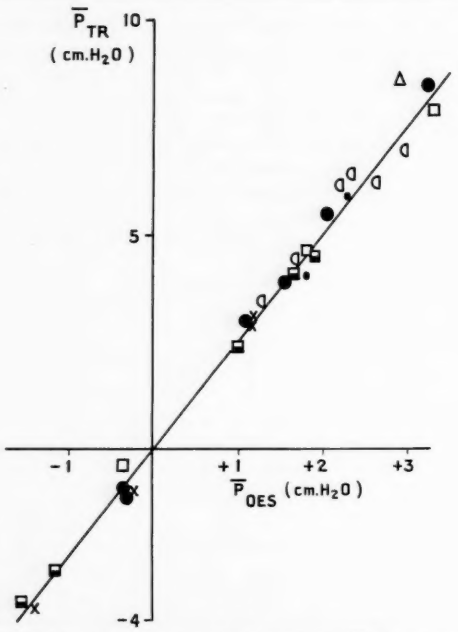

Fig. 5—Relation of mean tracheal pressure ($\overline{P}_{TR}$) to mean œsophageal pressure ($\overline{P}_{OES}$) with all respirators.

Chest-wall compliance has been adjusted to that of the "average" patient. Symbols as in fig. 3.

periphery and then by loss of circulating fluid into the tissue spaces (Otis et al. 1946, Barach et al. 1947, Henry et al. 1948). This loss of effective blood-volume takes time to develop; so a raised intrathoracic pressure which may be innocuous for short periods may not be so innocent if applied for longer.

When sitting and breathing against a constant pressure of about 27 cm. H_2O, some normal subjects faint within half an hour (Ernsting 1959). The airway pressure of 27 cm. H_2O, however, is not transmitted directly to the intrathoracic structures, for the functional residual capacity of the lungs is expanded by about 1·3 litres (Roxburgh and Ernsting 1957). Normal lung compliance is about 0·2 litre per cm. H_2O (Comroe et al. 1955) so that an increase of 1·3 litres in lung volume requires a pressure of 6·5 cm. H_2O to inflate the lungs. The remaining pressure, about 20 cm. H_2O (27−6·5 cm. H_2O) represents the increase in intrathoracic pressure.

In the paralysed patient receiving I.P.P.R. the mean intrathoracic pressure is above the resting level; in the normal subject the mean intrathoracic pressure is below it. Opie et al. (1959) found that the mean intrathoracic pressure in four normal supine subjects with a tidal volume of about 500 ml. and a respiratory frequency of about 16 per minute was on the average 2·4 cm. H_2O (range 0·8–2·8 cm. H_2O) below the resting level. With respirator 6 the mean intrathoracic pressure is 3·2 cm. H_2O above the resting value (fig. 4). Assuming that the resting levels in normal subjects and in these patients are comparable, the mean intrathoracic pressure in the patient receiving I.P.P.R. from respirator 6 is 5·6 cm. H_2O (3·2+2·4 cm. H_2O) above that of a normal supine subject.

It therefore appears that with at least one respirator (no. 6) set to provide the ventilation commonly used in clinical practice, the patient may have a rise in mean intrathoracic pressure of about 30% (5·6×100÷20) of that which will within 30 minutes cause syncope in a proportion of healthy seated subjects. Patients requiring I.P.P.R., however, are not healthy, and many may be unable to make use of the compensatory mechanisms available to the healthy subject, both because of muscular paralysis, and also because of impaired circulatory control, as in polyneuritis, barbiturate poisoning, or shock due to diminution of circulating blood-volume. They have, however, the advantage of lying flat most of the time, except when the physiotherapy required to keep the chest healthy entails their being tipped steeply head-up several times daily.

The rise in mean intrathoracic pressure, however, is only so large if inspiration has to be unduly prolonged because the rate of air-flow provided by the respirator is slow. In respirator 6, for instance, the peak inspiratory air-flow is only about 30 litres per min. With other respirators (1, 2, 3, 4, 5, 7A, 8A, and 9) mean intrathoracic pressure at the same ventilation (8 litres per min.) is raised by 3·5 to 4·0 cm. H_2O compared to the average healthy subject breathing spontaneously, and this is 17–20% of the rise which will cause syncope in a proportion of healthy subjects. With these respirators the inspiratory period can be kept short (one-third to one-quarter of the respiratory cycle) as the peak air-flow is faster—over 50–90 litres per minute. The inspiratory pressure wave-form influences the mean intrathoracic pressure and it is its duration rather than its precise configuration which is of particular importance.

In the patient receiving I.P.P.R., the venous return, obstructed during inspiration, probably takes place during expiration, and expiration should therefore be as free as possible. In the respirators tested the expiratory air-passages differed considerably in construction. For instance, after the expired air left the patient and before it was discharged from the apparatus it had to travel only 25 cm. in respirators 3 and 4, but it had to travel 200 cm. in respirator 5. Moreover, the bore of the expiratory tubing varied from 1·0 cm. (respirators 1, 2, 3, and 4) to 2·5 cm. (respirator 5). In spite of the differences in construction, however, there was little difference from one respirator to another in the mean œsophageal pressure during expiration. The reason for this is that in most apparatus it is not the tubing but the expiratory valve that forms the "bottleneck" and is the principle factor in determining rate of expiratory flow. In respirator 6, however, inspiration was so long that there was insufficient time for expiration to be completed.

In patients with chronic bronchitis, air may be trapped in the lungs because of collapse of the bronchi, and then subatmospheric pressure in the trachea may not reduce the intrathoracic pressure (Opie et al. 1959). Patients with respiratory paralysis, however, usually have healthy lungs when they fall ill, and in particular there is no weakening of their bronchial walls. In consequence, mean tracheal pressures below as well as above atmospheric pressure are linearly related to the mean intrathoracic pressure within the limits examined (fig. 5). The mean intrathoracic pressure can be reduced to near that in the normal subject, but to do this a subatmospheric pressure of 5–10 cm. H_2O must continue in the trachea throughout the greater part of the period between inspiration (figs. 1, 4).

Mean tracheal pressure will not, however, produce the same change in the mean intrathoracic pressure in all subjects. On the one hand, if the chest wall is less compliant than average, the mean intrathoracic pressure for a given tidal volume rises proportionately. This is particularly relevant in the treatment of severe tetanus, and supports our practice of paralysing such patients completely with a curare-like agent. On the other hand, if the lungs are unduly uncompliant, as when there is pulmonary consolidation or collapse, the tracheal pressure will not so readily be transmitted to the intrathoracic space. In these circumstances a much higher mean tracheal pressure may be called for, and, provided the tidal volume is not excessive, the mean intrathoracic pressure will not be unduly raised.

Summary

Intermittent positive-pressure respiration (I.P.P.R.) raises the intrathoracic pressure and obstructs the return of blood from the peripheral veins into the chest. The extent of this obstruction has been assessed in two patients with respiratory paralysis using 9 mechanical respirators designed for clinical use. The criterion of obstruction has been the rise in mean intrathoracic pressure caused by I.P.P.R.

When the tidal volume is 500 ml. and respiratory frequency is 16 per minute, the mean intrathoracic pressure is raised 3·5–5·9 cm. H_2O above that in the normal supine subject. The greatest rise seen is nearly 30% of that which will, within half an hour, produce syncope in a minority of normal seated subjects. A smaller rise in mean intrathoracic pressure (3·5–4·0 cm. H_2O) is associated with inspirations which last one-third or less of the respiratory cycle, and with a peak inspiratory air-flow of 50–90 litres per minute. Larger rises in mean intrathoracic pressure are due to slow rates of air-flow which entail a prolonged period of inspiration.

With the same tidal volume and respiratory rate, if a subatmospheric (" negative ") pressure of 5–10 cm. H_2O is applied to the trachea between inspirations, the mean intrathoracic pressure can be reduced almost to that in the normal subject breathing spontaneously. To achieve this, subatmospheric pressure must continue throughout almost the whole of the period between inspirations.

The mean intrathoracic pressure is linearly related to the mean tracheal pressure with all respirators.

We wish to thank Dr. W. Ritchie Russell for continued encouragement; Dr. D. J. C. Cunningham, Dr. Grant Lee, and Squadron-Leader John Ernsting for helpful advice; and Sister Mair for cooperation and assistance. Dr. W. H. Kelleher and Dr. W. F. T. McMath were kind enough to lend respirators for this investigation.

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Appendix

Respirator no.	Type
1, 2	Radcliffe positive-negative pressure respiration pump. In respirator 1, inspiration was 23% of the total respiratory cycle; in respirator 2, it was 30%. 1A and 2A positive pressure only; 1B and 2B with negative pressure.
3, 4	' Beaver ', models 1 and 2 respectively. For the purposes of this investigation the 2 models were identical.
5	Engstrom. 5A positive pressure only; 5B with negative pressure.
6	Obsolescent model which has been commercially available for a number of years.
7	Smith Clarke. 7A positive pressure only; 7B with negative pressure.
8	' Pneumotron '. 8A inspiration 20% of respiratory cycle; 8B inspiration 55% of respiratory cycle.
9	A prototype respirator kindly lent by Prof. E. A. Pask for this investigation. 9A at low tidal volume; 9B at high tidal volume.

The letters A and B after the number of each respirator refer to the labelling of the tracings in figs. 1–5.

MULTIPLE SCLEROSIS

A TRIAL OF TREATMENT WITH TOLBUTAMIDE

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THIS study arose from the chance finding of Sawyer (1960) that the administration of tolbutamide to one of his patients for the treatment of acne was followed by remission of the symptoms of coexisting multiple sclerosis. This led him to try the drug in seven further patients with chronic multiple sclerosis: in each case definite and rapid improvement in symptoms and signs was observed. Deterioration followed both the substitution of tolbutamide for placebo capsules and the institution of a high as opposed to a low or normal intake of dietary carbohydrate.

Sawyer suggested that these results lent support to the views of Jones et al. (1950), Lowry et al. (1953), and Henneman (1954). On the basis of detectable abnormalities of glucose tolerance, and of serum-pyruvate, lactic-acid, and α-ketoglutaric-acid levels in patients with multiple sclerosis, these workers postulated a biochemical block in the carbohydrate metabolic process at the pyruvic/lactid-acid level, or defective metabolism of small fractions of carbohydrate. Under such circumstances the hypoglycæmic effect of tolbutamide might be expected to alter the course of the disease.

We here report the results of a controlled trial of tolbutamide in multiple sclerosis.

Method

Forty patients were admitted to the trial. They were selected from a large series at present under epidemiological study in the Tyneside area. The patients were moderately disabled by the disease, and they fell into the functional grades II–IV described by Miller et al. (1961). Tolbutamide tablets of 500 mg. were used, together with dummy tablets of identical shape and size. The dose of tolbutamide was 500 mg. three times per day, and the same number of dummy tablets were taken by the patients

TABLE I—COMPARISON OF GROUPS BEFORE TREATMENT

—	Treatment	
	Tolbutamide	Dummy
No. of patients	20	20
Males	6	7
Females	14	13
Mean age	41·5	41·0
Mean age at onset	34·1	29·9
Course of disease in previous 6 months:		
Progressive	5	5
Static	13	15
Improving	2	0
Average severity (Alexander)	171	218
Functional grade (see text):		
II	4	4
III	12	12
IV	4	4

in the control group. No alterations to the patients' usual diets were imposed during this investigation.

Twenty patients were allocated to the tolbutamide group, and twenty had dummy tablets, using a restricted randomisation scheme which guaranteed approximately equal numbers of each age and sex, and also took into account the severity of the disease. In no instance did side-effects cause the withdrawal of patients from the trial, and no patient defaulted during the 3 months of the trial. In one man, however, increasingly severe paraplegia necessitated admission to hospital for intrathecal phenol treatment in the 3rd month. An independent observer kept the patients taking tolbutamide under surveillance in order to detect any side-effects.

Assessment

Table I sets out the composition of the two groups—their mean age, mean duration of disease, previous medication, and average severity (Alexander et al. 1958). No patient was admitted to the trial who had been included in previous therapeutic observations, or who had received other than symptomatic treatment.

Each patient was examined on the day he or she entered the trial, after 28 days' treatment, and finally at 3 months. The examiner was unaware whether the patient was taking tolbutamide or dummy tablets. Each was assessed according to the numerical scoring system of Alexander et al. (1958).

Specific inquiry was made regarding acute exacerbations or new symptoms, and each patient was asked if he considered himself to be improved by the tablets, made worse, or unchanged.

Comparison of Patient Groups

Before Treatment

The groups were similar before treatment, as shown in table I. The ages ranged from 21 to 60, with an average of 42 for the tolbutamide group and 41 for the control group. The mean ages at onset were 34 and 30 respectively. The difference, which is not statistically significant, can be explained by the fact that two patients, both with a very late onset (ages 56 and 64), fell into the group having tolbutamide.

The functional gradings, as designed, were exactly the same for the two groups, and the Alexander scores for severity did not differ significantly. The difference between 171 and 218 may appear large, but individual scores ranged from 7 to 547. The method of analysis of the effect of treatment depends on the differences between Alexander scores before and after treatment, and is designed to minimise the effect of differences between the condition of patients on admission to the trial.

TABLE II—COMPARISON OF GROUPS AFTER 1 MONTH

—	Treatment	
	Tolbutamide	Dummy
Average change in Alexander score after 1 month	+6·05	−0·9
Patients' assessment of condition after 1 month:		
Better	4	3
Unchanged	10	11
Worse	6	6

After 1 Month

Alexander scores.—Results are given in terms of differences from the initial score (table II). A positive difference indicates deterioration, and a negative difference improvement, in the patient's condition. An indication of the variable severity of disablement over the 1st month is given by the fact that one patient had improved by 95 points, while another had deteriorated by 78 points. On the average, however, there was very little change with either treatment. Patients having tolbutamide deteriorated by an average of 6 points, while those having dummy treatment improved by 1 point. The standard error of each of these averages is ±9 points. Thus neither figure differs significantly from zero (no change over 1 month) nor do they differ from each other.

After 3 Months

Results are again given in terms of differences from the patient's initial score, a positive difference indicating deterioration, and a negative difference improvement.

Disablement had again shown considerable fluctuation. The patient having tolbutamide, who had improved by 95 points in the 1st month, maintained this improvement at 3 months. Another, relatively unchanged at 1 month, had deteriorated by 118 points at 3 months. These are the two extreme cases. On the average, however, there was very little change with either treatment.

The results are shown in table III. Patients having tolbutamide had deteriorated by an average of 6 points at the end of 1 month, and after 3 months had returned to the same average score as before treatment. Patients having dummy treatment had improved by 1 point after 1 month, and by 7 points at the end of 3 months. As will be seen by the standard errors, none of these changes differed significantly from zero.

TABLE III—COMPARISON OF GROUPS AFTER 3 MONTHS

—	Treatment	
	Tolbutamide	Dummy
Average change in Alexander score:		
After 1 month	+6·05±9·0	−0·90±8·1
„ 3 months	+0·05±9·6	−6·55±4·6
Patients' assessment of condition after 1 month:		
Better	4	2
Unchanged	10	11
Worse	5	8

A positive change indicates deterioration; a negative change indicates improvement.

It is of some interest that of the twenty patients on dummy treatment, the Alexander score had improved in fourteen at the end of 3 months, while five had deteriorated and one had been admitted to hospital for other treatment which precluded assessment. Although functional improvement was small in many of these cases, the result approaches statistical significance for the efficacy of dummy treatment.

When the average changes in Alexander scores for the two treatments are compared directly, there is no significant difference. The patients having dummy tablets were, on average, better by 7 points than the tolbutamide patients both after 1 and after 3 months, but the standard errors of the differences were ±12 and ±11.

Patients' Assessment after 1 Month

The results set out in table II show that six patients in each felt worse at the end of a month; four and three felt better in the tolbutamide and dummy groups respectively. There was very little correlation between the patients' impression and their Alexander scores. The patient who improved by 95 points said that he was unchanged, and several patients who felt worse showed functional improvement by Alexander's criteria.

Patients' Assessment after 3 Months

Again there was little correlation between the patient's impression and his Alexander score; four felt better with

tolbutamide, and two with dummy tablets; five felt worse with tolbutamide, and eight with dummy tablets.

Conclusions

This trial has yielded no evidence to support the claim that patients with multiple sclerosis are benefited by tolbutamide. There is a wide scatter in individual scores, and considerable variability in the apparent results of the two treatments. Although on the average the dummy treatment seems to have been somewhat more beneficial than tolbutamide, neither was statistically significant. The cases having tolbutamide revealed the wider range of response, including the two " best " as well as the two " worst " responses to treatment. We do not consider that this finding is likely to have any biological significance, and in any case it furnishes no basis for the use of tolbutamide as a form of treatment.

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SKELETAL MATURATION IN OVARIAN DYSGENESIS AND TURNER'S SYNDROME

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SENIOR LECTURER IN SOCIAL AND PREVENTIVE MEDICINE AT GUY'S HOSPITAL AND THE LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

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Turner's syndrome has been accorded a great deal of attention in the past few years, largely as a result of recent advances in cytological technique. Apart from such bearing as it has on genetic theory, the syndrome is of interest from the point of view of physical development, because it gives some indications of the nature of the endocrine influences on somatic and skeletal growth and maturation at puberty. The present paper is concerned with skeletal maturation, and a comparison is made between patients with ovarian dysgenesis or Turner's syndrome and two other groups of children whose skeletal maturation was thought to be slowed as a result of adverse environment.

Material and Method

Case Group

The case material consists of 25 patients, aged from 12 to 27 years, in whom the diagnosis of ovarian dysgenesis or Turner's syndrome was confirmed cytologically (Bishop et al. 1960). Table I gives details of the diagnostic criteria and other pertinent information. The radiographic records of each of them include a posteroanterior radiograph of the hand and wrist, and for 5 there are also anteroposterior and lateral radiographs of the knee-joint.

Comparison Groups

The two groups of children who were compared with the cases of ovarian dysgenesis (case group) were:

1. 39 girls who had been in a German residential school during and immediately after the war, and who had been studied by a Medical Research Council unit (Widdowson and McCance 1954, Berridge and Prior, 1954). Only records taken at the outset of the study were used, at which time the girls' ages ranged from $4^1/_2$ to $14^1/_2$ years, and all of them were in a state of chronic undernourishment. Hand films only were available for this group.

2. 13 girls who were either suffering from active tuberculous meningitis or had recently recovered from the disease. Hand films were included in the records of all these girls, and for 11 of them there were also radiographs of the knee. Table II shows details of the ages of the three groups.

Assessment of Films

78 of the 93 films were assessed by both of us; 15 (6 knee and 9 hand) were not traced until after one of us had left the country, and so only the assessments of A. are included. The 78 films were assessed four times in all, twice by each of us; and the remaining 15 were assessed twice by assessor A. On every occasion the films were read in a random order and the assessor was ignorant of the age of the child. For the ovarian dysgenesis and tuberculous meningitis cases this was a simple matter because the age of the child did not appear on the film. For the German children, whose films bore their ages, these ages were obscured. The hand films were assessed against the Todd (1937) standards and the knee films against those of Pyle and Hoerr (1955). The two readings of each assessor were then averaged, giving one value for assessor A. and one for assessor Z. for each film.

Results

The averages of the two readings of each assessor of each film for the hand X-rays of the case group (figs. 1 and 2) show that the pattern is that of an increasing difference from the standard development of healthy American girls after the age of 10. Furthermore, though the average boy matures skeletally more slowly than the average girl, over the age-range being studied, those with ovarian dysgenesis mature much more slowly than the boys' normal standard and the difference tends to be greatest among the oldest patients. The same general pattern was found for the knee (fig. 3). Table I shows that while the 4 patients with mature hands (cases 2, 11, 13, and 24) had received at least 3 years' treatment before X-ray, only 2 patients (5 and 21) had received treatment for any length of time without having a mature hand. Case 21 was a mosaic (XO/XX) and was chromatin-positive, whereas the other 4 (2, 11, 13, and 24) were all chromatin-negative. The cytological characteristics of case 5 are now being restudied.

In contrast, though the other two groups are also retarded in their skeletal maturation, this is a general phenomenon throughout the entire age-range; there is no suggestion of increasing retardation dating from the immediate prepubertal period (figs. 4, 5). A series of summarised comparisons between the patients in the case group and the other two groups is shown in tables II–V. In order to prepare these, the assessments of A. and Z. have been kept separate, and for each patient the chronological age has been subtracted from the mean of the two skeletal-age assessments. These differences have then been averaged for each of the three groups, and the standard errors of the group averages calculated. Table III shows that, though assessor Z.'s assessment of skeletal age tended to be about 3 months lower than those of assessor A., this difference was more or less constant for the three groups and both assessors considered the average retardation for the case group to be more than twice as great as that of the other two groups. Similar calculations for the knee are shown in table IV. In terms of the anatomical state of the bones involved, the case group ossify their carpal bones at a rate approaching the normal, and the epiphyses of their metacarpals fuse, if anything a little early—particularly in those cases which show brachymetacarpalism. The epiphyses of the phalanges, of the distal ends of the radius and ulna, and of the femur and tibia at the knee seem, however, to delay fusion in those cases not treated with œstrogens.

The comparison between the three groups and the boys'

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TABLE I—CLINICAL DETAILS OF 25 CASES OF OVARIAN DYSGENESIS AND TURNER'S SYNDROME

Case no.	Age (yrs.)	Barr sex bodies	Somatic group	Highest F.S.H.	17-K.S.	Chromosomal findings		X-ray		Treatment		
						No.	Type	Chronological age (yrs. mos.)	Skeletal age† (yrs. mos.)	Age at onset	Nature	Effect
1•	14	–	O.D.	>40	<2	45	XO	15·5	13·0	14	Œstrogens	S.S.C. M.
2	17	–	T.S.	96	2·7	Not known		21·1	16·3	18	Stilbœstrol	S.S.C. M.
3•	8	–	T.S.	..	..	,,	,,	12·3	9·6	13	Anabolic steroid	Nil to date
4•	13	–	O.D.	>24	..	,,	,,	13·7	12·0	..	Nil	..
5	18	–	T.S.	96	7·8	45	XO	21·11	12·3	18	Stilbœstrol. Progesterone	S.S.C. M.
6	17	–	O.D.	96	3·0	Not known		17·9	11·9	17	Stilbœstrol. Progesterone	S.S.C. M.
7	17	–	T.S.	..	2·7	,,	,,	16·8	13·3	17	Stilbœstrol	S.S.C. M.
8	17	–	O.D.	96	4·8	,,	,,	18·9	13·3	18	Testosterone	Body hair only
9•	15	..	O.D.	>384	2·6	,,	,,	15·2	13·6	15	Œstrogen	Nil to date
10	20	..	O.D.	96	7·5	,,	,,	22·0	13·9	..	Nil	..
11	22	–	O.D.	<8	5·7	,,	,,	25·4	16·3	17	Stilbœstrol	S.S.C. M.
12	27	..	O.D.	>96	3·1	,,	,,	26·8	14·0	27	Stilbœstrol	Nil to date
13	21	–	O.D.	360	4·4	,,	,,	25·11	16·3	21	Stilbœstrol. Progesterone	S.S.C. M.
14•	14	–	O.D.	32	10·8	45	XO	13·9	10·9	14	Stilbœstrol. Progesterone	S.S.C. M.
15	16	+	O.D.	384	..	Not known		16·2	13·3	16	Stilbœstrol. Testosterone	Nil
16	17	–	O.D.	96	11·7	45	XO	18·3	13·9	17	Œstrogens	S.S.C. M.
17•	<16	–	T.S.	96	2·6	45	XO	13·7	11·0	14	Œstrogens. Testosterone	S.S.C. M.
18•	14	–	T.S.	384	1·9	Not known		15·7	12·6	16	Œstrogen	S.S.C. M.
19	18	+	O.D.	360	5·1	75% 45 / 25% 46	XO/XX	18·9	13·6	19	Œstrogen. Stilbœstrol	S.S.C. M.
20•	14	+	O.D.	>24	4·8	Not known		17·3	14·0	17	Œstrogen. Testosterone	S.S.C. M.
21	16	+	O.D.	96	4·7	66% 45 / 33% 46	XO/XX	21·3	13·9	17	Stilbœstrol. Progesterone	S.S.C. M.
22	18	+	O.D.	96	..	Not known		17·10	12·6	18	Stilbœstrol	S.S.C. M.
23	15	+	O.D.	64	5·7	25% 45 / 75% 46	XX/XO	17·1	13·9	17	Œstrodial	Breasts only M.
24	19	–	T.S.	96	11·3	Not known		27·0	16·3	19	Œstrogen. Progesterone	S.S.C. M.
25	19	+	O.D.	>24	3·3	,,	,,	25·10	13·9	25	Œstrogen. Progesterone	S.S.C. M.

O.D. = Ovarian dysgenesis.
F.S.H. = Follicle-stimulating hormone.
T.S. = Turner's syndrome.
17-K.S. = 17-ketosteroids.
S.S.C. = Development of secondary sexual characters.
M. = Menstruation.

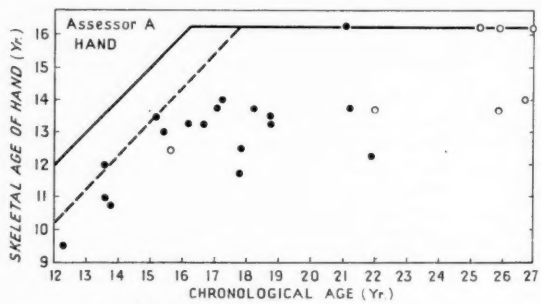
• = Cases not aged 16 at onset of treatment; in all other cases, except no. 5, primary amenorrhœa was reported.
† = Skeletal-age assessments in this table are the hand evaluations of assessor A.
– = No Barr body.
+ = One Barr body.

standard, shown in table v, has been made with the help of a table published by Todd (1937) giving a list of the male standard plates which are equivalent to the female standard plates. In this way male skeletal age has been substituted for each female skeletal age and the group averages have been recalculated. In the opinion of both assessors, patients in the case group over the age-range being studied mature more slowly than the normal *boy*. While observer A. thought that the undernourished girls were over 6 months slower in their maturation than normal boys, observer Z. did not think that their maturation was significantly slower than boys. Neither assessor thought that the tuberculous-meningitis group differed significantly in their rate of maturation from normal boys.

The skeletal-age technique of assessing skeletal maturation is the only inspectional one available for the hand or knee through the entire age-range; it has, however, theoretical shortcomings (Acheson 1954, Acheson and Hewitt 1954, Falkner 1958), and among these is the fact that the age of maturity differs for each part of the body within each sex, as well as differing for a given part of the body between the sexes. For instance, in Todd's (1937) standards, the hand is considered mature in boys at $18^3/_4$ years and in girls at $16^1/_4$ years, while equivalent ages for the knee are 18 years for boys and $15^1/_2$ years for girls (Pyle and Hoerr 1955). An additional difficulty, which has special relevance to the present data, is that a patient whose epiphyses remain ununited with the diaphyses increases her retardation in skeletal years as she gets progressively older than the normal age of achieving maturity. For instance, a patient (case 12), whose chronological age was nearly 27, was considered to have a skeletal age of 14 for both hand and knee, thus giving her a retardation figure of 13 years for each. In all, 18 of the 25 patients in the case group were over the age at which a normal girl's hand achieves maturity; and 3 of the 5 patients who had had X-rays taken of the knee were over the normal age this joint becomes mature in girls. This would certainly exaggerate the mean differences shown in table III. To correct for such exaggeration, and to make the case group more strictly comparable with the other two groups (all members of both of the comparison groups being younger than the normal age of maturity), the oldest patients were taken as having a chronological age of $16^1/_4$ or $15^1/_2$, as the case might be. Thus, the retardation in case 12 was reduced from 13 years for both joints to $14–16^1/_4 = -2^1/_4$ years for the hand and $14–15^1/_2 = -1^1/_2$ years for the knee. The 4 cases with mature hands were included in the analysis because, though there is strong presumptive evidence that treatment caused the closure, we cannot be certain because no X-rays were taken before treatment was started. The results of this analysis are shown in table VI; the differences between the Turner's group and normal girls' standards are still greater than those for the other two groups shown in table III.

TABLE II—AGES OF CASE AND COMPARISON GROUPS

Group	Cases	Age (yrs.)		
		Mean	S.D.	Range
Ovarian dysgenesis and Turner's syndrome	25	19·1	4·5	12–27
Undernourished girls	39	9·7	2·7	$4^1/_2$–$14^1/_2$
Tuberculous meningitis girls ..	13	10·3	3·4	3–16



Female norm.
Male norm (calculated) in terms of female standards.
• Cases available to assessors A and Z.
○ Cases available to assessor A only.

Fig. 1—Ovarian dysgenesis and Turner's syndrome. Distribution of assessor A's evaluation of skeletal age, assessed from the female hand standards of Todd, against chronological age.

Note that although 20 of the 25 cases are actually over $13^1/_2$ years of age the skeletal age of only 4 is in excess of 14 years; all of these 4 had received at least 3 years' treatment with œstrogen.

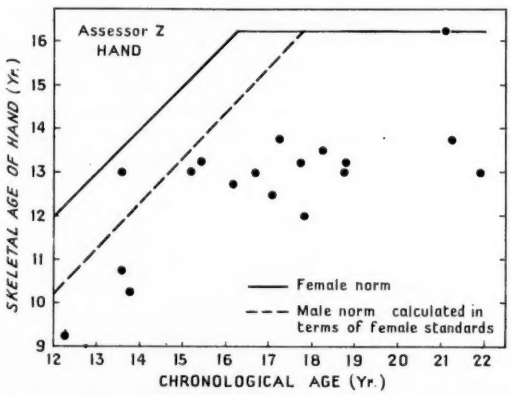


Fig. 2—Ovarian dysgenesis and Turner's syndrome. Assessor Z's evaluation of skeletal age (hand) in 18 of the 25 cases shown in fig. 1.

Discussion

Before discussing the results it is appropriate to consider how valid are standards compiled from the developmental records of prosperous American children before the war as a basis for studying children in postwar Europe.

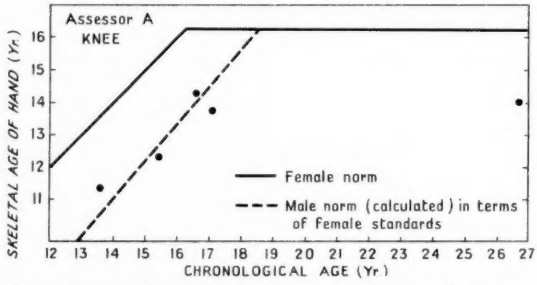


Fig. 3—Ovarian dysgenesis and Turner's syndrome. Skeletal age (knee) for five of the 25 cases shown in fig. 1. The distribution is similar in pattern.

The Todd (1937) atlas was used to assess hand films taken repeatedly over the first 5 years of life of over 500 Oxford children between 1943 and 1951, and it was found that the mean skeletal age of the English girls at that time was a little below the American standards (Acheson, Kemp, and Parfit 1955).

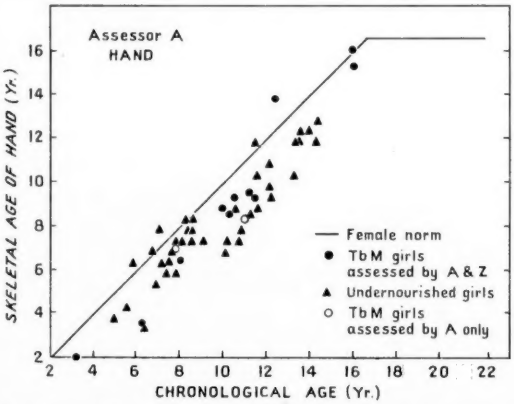


Fig. 4—Comparison group. Assessor A's evaluation of skeletal age (hand) of 52 girls, who were either suffering from chronic undernourishment or chronic illness, plotted against chronological age.

Note that in contrast to figs. 1–3, where the cases tend to veer away from the female norm, these cases tend to converge upon it.

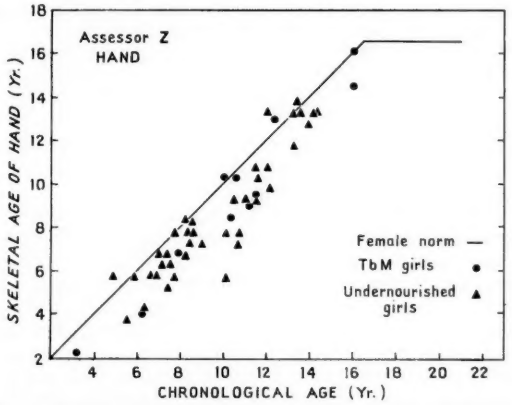


Fig. 5—Comparison group. Assessor Z's evaluation of the skeletal age of 50 of the 52 girls shown in fig. 4.

More recently the same standards have been found to compare satisfactorily with a group of Welsh children of both sexes whose ages vary from 2 years to maturity (Acheson and Fowler, unpublished data). Though the Todd atlas has since been revised and greatly improved twice (Greulich and Pyle 1950, 1959), the original was used for two reasons: (1) it alone had been used in the Oxford Child Health Survey and therefore its comparability with healthy European populations was known, and (2) it was the basis of the skeletal-age assessments in Simmons' (1944) monograph, to which reference is made later. To our knowledge nothing has been published about the Pyle and Hoerr knee standards from European experience, but they are compiled from the same population as the Todd hand atlas, and therefore should be equally applicable.

Figs. 1–3 suggest that the skeletal maturation of the case group, with 4 exceptions of whom more later, becomes arrested at a skeletal age of 13¾ years. The mean age of menarche in the Brush Foundation Study girls in Cleveland, Ohio, whose median maturation the Todd and Hoerr–Pyle standards represent, was 12 years 7 months, and their mean skeletal age at menarche, 13 years 1 month (Simmons 1944). Thus, the majority of these cases show an arrest in their skeletal maturation which is in very close parallel with their arrest in sexual maturation.

TABLE III—HAND: DIFFERENCE IN YEARS BETWEEN SKELETAL AGE TODD (GIRLS' STANDARD) AND CHRONOLOGICAL AGE

Group	Assessor A			Assessor Z		
	n	Mean	S.E.	n	Mean	S.E.
Ovarian dysgenesis and Turner's syndrome ..	25	−5·80	0·69	18	−4·30	0·46
Undernourished ..	39	−1·53	0·17	39	−1·20	0·18
Tuberculous meningitis	13	−1·23	0·30	11	−0·94	0·31

A similar conclusion has been drawn from a study of 25 patients with "gonadal dysgenesis" in Holland by van der Werff ten Bosch (1959a, 1960), who used the skeletal age standards of Speijer (1950) and found that for his cases "skeletal [maturation] is normal till the age of puberty and lags behind progressively from about that time" (van der Werff ten Bosch 1959a). None of the cases in the present series was seen sufficiently early to confirm the normality of skeletal maturation in the first 10 years of life. Tanner et al. (1959) report 16 cases of Turner's syndrome who are chromatin-negative, and conclude that "XO individuals [have] a rate [of skeletal maturation] corresponding to XX." This conclusion is certainly in accord with that of van der Werff ten Bosch (1959a) for the first 10 years of life; it is at complete variance, however, with his and our findings for development from the immediate prepubertal period onwards.

TABLE IV—KNEE: DIFFERENCE IN YEARS BETWEEN SKELETAL AGE PYLE AND HOERR (GIRLS' STANDARD) AND CHRONOLOGICAL AGE

Group	Assessor A			Assessor Z		
	n	Mean	S.E.	n	Mean	S.E.
Ovarian dysgenesis and Turner's syndrome ..	5	−4·73	1·78	..	..	..
Tuberculous meningitis	11	−1·02	0·21	10	−1·78	0·34

The pattern for the other two groups, one of which had been exposed to chronic undernutrition and the other had had a chronic illness, is essentially different for two reasons: (1) there is no doubt that there is a general retardation long before the prepubertal stage, and (2) this retardation shows no evidence of increasing after the prepubertal period—in fact, it seems to decrease. Thus, the retardation in gonadal dysgenesis and in Turner's syndrome appears to have a pattern of its own, differing from the retardation induced by environmental causes.

In an earlier study of the maturation of the hip-joint and pelvis in which the Oxford method of assessing skeletal maturity was used—which measures maturation against a points scale instead of using time as a yardstick—skeletal maturation in the hip and pelvis, at least, seemed to undergo a preadolescent spurt (Acheson 1957). A further analysis of the data, together with a critical review of published work on the hand and knee, confirmed this belief (Hewitt and Acheson 1961a and b), and it was concluded that the steroid sex hormones, in addition to

TABLE V—HAND: DIFFERENCE IN YEARS BETWEEN SKELETAL AGE TODD (BOYS' STANDARD) AND CHRONOLOGICAL AGE

Group	Assessor A			Assessor Z		
	n	Mean	S.E.	n	Mean	S.E.
Ovarian dysgenesis and Turner's syndrome ..	25	−4·14	0·67	18	−2·80	0·47
Undernourished ..	39	−0·71	0·19	39	−0·39	0·21
Tuberculous meningitis	13	−0·23	0·38	11	+0·21	0·42

accelerating growth, accelerate the final stages of skeletal maturation, including epiphyseal closure. It was argued that in both sexes androgens were probably responsible for this phenomenon, and that in the female these probably originated from the adrenal cortex. The data reported here indicate that this conclusion may have to be revised and that the hormones responsible for epiphyseal closure in the female may be ovarian in origin; furthermore, the fact that the only mature hands were to be found among those who had received stilbœstrol or œstrogen for 3 years suggests that female sex hormones may play a part in skeletal maturation.

The brachymetacarpalism in gonadal dysgenesis, referred to by van der Werff ten Bosch (1959b), is due to premature epiphyseal fusion in the affected bones. Because these bones are different in their developmental behaviour from those elsewhere in the hand, and most of the others in the body, the fusion in their case is unlikely to be hormonally induced, but is more probably due to an abnormality in the cartilaginous anlage of the bones themselves (Acheson 1959). This tendency for the carpals to behave differently from the phalanges and the radius and ulna may explain the statement, which occurs repeatedly in the literature, that " bone age in Turner's syndrome is normal," for a common practice is to assess " bone age " from a radiograph of the wrist alone. Such an X-ray would, of course, in most of the present cases, show fully ossified—though irregularly shaped—carpals together with mature metacarpals but would fail to show the immature radius, ulna, and phalanges.

TABLE VI—HAND AND KNEE: DIFFERENCE IN YEARS BETWEEN SKELETAL AGE (GIRLS' STANDARD) AND CHRONOLOGICAL AGE, TAKING $16^1/_4$ AS A MAXIMUM FOR THE HAND AND $15^1/_2$ FOR THE KNEE

Group	Hand						Knee		
	Assessor A			Assessor Z			Assessor A		
	n	Mean	S.E.	n	Mean	S.E.	n	Mean	S.E.
Ovarian dysgenesis and Turner's syndrome ..	25	−2·32	0·24	18	−2·70	0·24	5	−1·97	0·29

Though the present data do not appear to lend direct support to the suggestion made by Tanner et al. (1959) that the Y chromosome is responsible for the slower skeletal maturation of the male, they do not necessarily refute it.

Summary

The skeletal age (hand) of 25 cases of gonadal dysgenesis (all female in phenotype) was assessed twice by each of two observers, each assessment being made independently from the others, and in ignorance of the chronological age of the patient. In 14 of the 18 (78%), whose age was equal to or in excess of that at which the hand of the normal is mature, the majority of the epiphyses remained unclosed; a similar pattern was observed in the 5 cases for whom knee films were available. All the 4 girls who achieved skeletal maturity had been taking œstrogens for at least 3 years before being radiographed; only 2 of the other 14 had been taking them for an equivalent time. This pattern of increasing deviation from the normal among girls who should be adolescent was in contrast to retardation caused by chronic undernutrition or chronic illness in a comparison group of 52 girls, for in them the degree of retardation tended to be less after the age of 14 than in the younger groups.

We are deeply indebted to the following for allowing us to study their material and to publish the results: the cases of gonadal dysgenesis and Turner's syndrome, Dr. P. M. F. Bishop and Prof. P. E. Polani, Guy's Hospital; the cases of undernutrition, Dr. Berridge, Addenbrooke's Hospital, Cambridge, and Dr. Elsie Widdowson, M.R.C. Experimental Medicine Unit, Cambridge; and the cases of tuberculous meningitis, Dr. Honor Smith, Radcliffe Infirmary, Oxford. Miss Gillian Fowler, whose work is supported by the Medical Research Council, kindly helped with the analysis of the data, and Professor Polani devoted much time to discussing and criticising our study.

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Preliminary Communication

CHLORHEXIDINE AS THE PROBABLE CAUSE OF AN INCREASE IN PROTEUS RETTGERI INFECTIONS OF THE URINARY TRACT

DURING the past 4 years *Proteus rettgeri* has been isolated in our laboratory from the urine of ninety patients and from the blood of two patients. Because all the patients had undergone catheterisation, cystoscopy, or treatment with an indwelling catheter before the infection appeared, these must be regarded as hospital infections, as already pointed out by Omland.[1]

Urinary-tract infections caused by *Pr. rettgeri* are serious infections. Like all other proteus species these bacteria are capable of splitting urea to form ammonia. Infection with these organisms is characterised by alkaline urine and frequent stone formation, and in contrast to other proteus species *Pr. rettgeri* is very resistant to antibacterial agents.

In our laboratory the combination of kanamycin (or neomycin) with tetracycline was found to have a true synergistic effect on these organisms. The action of kanamycin 50 μg. per ml. with tetracycline 20 μg. per ml. was bactericidal in vitro in all strains investigated, although such concentrations of either antibiotic alone were ineffective. Treatment with daily injections of kanamycin 0·5 g. intramuscularly and tetracycline 250 mg. q.d.s. by mouth gave good results, except when renal stones were present.

On investigating the source of these infections we found that the growth of *Pr. rettgeri* is not inhibited by the concentration of chlorhexidine ('Hibitane') used in our urological ward (i.e., 1/5000).

METHODS

To tubes containing broth at pH 7·5 chlorhexidine digluconate was added to give various concentrations in a volume of 0·5 ml. Each tube was inoculated with 0·5 ml of a 1/1000 dilution of an 18-hour broth culture of the investigated strain. The final concentrations of chlorhexidine digluconate ranged from 1/2000 to 1/256,000. After 48 hours' incubation at 37°C the turbidity was recorded for each tube. From tubes remaining clear one loopful was subcultured on to a blood-agar plate, and these plates were incubated for another 24 hours. The lowest concentration of chlorhexidine in the tube, when after 48 hours no turbidity was present and no colonies were grown on subculture, was recorded as the minimum bactericidal concentration.

Most strains were investigated twice. Other methods of inoculation gave the same results, but the size of the inoculum had a definite influence on the results. Inoculation with a 1/100 or 1/10 dilution of the broth culture made bacteria grow in a concentration of chlorhexidine twice or four times higher than did inoculation with a 1/1000 dilution.

Of the 58 investigated strains all were freshly isolated from urine, except one strain of *Pr. vulgaris*, which was very sensitive to chlorhexidine (see table).

SENSITIVITY OF ORGANISMS TO CHLORHEXIDINE

—	Number of strains	Minimum bactericidal concentration of chlorhexidine after 48 hours at 37°C							
		1/2000	1/4000	1/8000	1/16,000	1/32,000	1/64,000	1/128,000	1/256,000
Proteus rettgeri ..	15	1	3	7	4	..	..	..	..
„ *mirabilis* ..	16	2	9	5	..	..	..	..	..
„ *vulgaris* ..	4	..	2	1	..	..	..	1	..
Pseudomonas pyocyanea	8	..	..	..	2	6	..	..	..
Escherichia coli ..	7	..	..	..	..	..	1	3	3
Aerobacter	2	..	..	..	..	2	..	..	..
Staphylococcus albus ..	2	..	..	..	..	..	..	..	2
„ *aureus* ..	2	..	..	..	..	..	..	..	2
Streptococcus fæcalis ..	2	..	..	..	..	..	2	..	..

Of the 58 investigated strains all were freshly isolated from urine, except one strain of *Pr. vulgaris*, which was very sensitive to chlorhexidine (see table).

RESULTS

The sensitivity of different strains of the same bacterial species showed considerable variation, but there was a definite distinction between the rather insensitive proteus species and other pathogens of the urinary tract. Nearly all strains of *Pr. rettgeri*, *Pr. mirabilis*, and *Pr. vulgaris* were insensitive to a concentration of 1/8000 or less. Only 1 non-swarming strain of *Pr. vulgaris*, conserved for years in the laboratory, was very sensitive to chlorhexidine. *Pr. morgani* could not be investigated. *Pseudomonas pyocyanea* was moderately sensitive. *Escherichia coli* and other bacteria were very sensitive.

We have not been able to find any report of the analysis of the sensitivity of the different proteus species to chlorhexidine. Our other results correspond with those of Davies et al.,[2] Calman and Murray,[3] and Beeuwkes.[4]

The addition of chlorhexidine in a concentration of 1/10000 proved to be a selective culture medium for the isolation of *Pr. mirabilis* from fæces.

DISCUSSION

Before 1957 *Pr. rettgeri* was seldom isolated in our laboratory. Since 1957 chlorhexidine has been used regularly as an antiseptic in our urological ward. From our investigation we assume that the increase in *Pr. rettgeri* urinary infections is connected with the use of chlorhexidine. We could not be certain whether the number of infections with other species of proteus has also been increasing over these years.

The use of chlorhexidine in urology was advocated by Beeuwkes and de Vries.[5] Chlorhexidine has been generally employed in urology since 1956, and it is the only antiseptic used in our urological ward. Beeuwkes and Vries recommended a 1/5000 solution for irrigation of the bladder. The same concentration was used after gynæcological operations by Paterson et al.[6] Higher concentrations are unsuitable for bladder lavage because they irritate the mucosa. A 1/2000 solution in glycerin may be used to disinfect the urethra.[7]

Most strains of proteus, however, are insensitive to a 1/5000 solution of chlorhexidine, and some strains even to a 1/2000 solution. Moreover, the activity of chlorhexidine is less in the presence of pus. Concentrations higher than those we mention are necessary with heavy contamination. In clinical practice chlorhexidine will remain in the bladder or the urethra for only a short time, but our results were determined after 48 hours. Although *Ps. pyocyanea* is more sensitive to chlorhexidine than is proteus, *Ps. pyocyanea* was often present in urinary-tract infections in our hospital despite the use of chlorhexidine. In particular infections with *Ps. pyocyanea* combined with *Pr. rettgeri* were frequent.

Not only infections with *Ps. pyocyanea* and *Pr. rettgeri* but also most infections with *Pr. mirabilis* and *Pr. vulgaris* are hospital infections.[8,9] It seems to us that the use of

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an antiseptic which is ineffective against serious hospital infections of the urinary tract should be abandoned in urological departments.

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Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS

THE 66th general meeting of the association was held in Glasgow on April 13 and 14 under the presidency of Prof. D. F. CAPPELL. The proceedings included three symposia: on chromosome abnormalities (under the chairmanship of Prof. W. M. DAVIDSON); on staphylococcal infections (Prof. J. W. HOWIE); and on immunopathology (Dr. BRUCE CRUICKSHANK). We publish below summaries of some of the contributions.

Chromosomal Abnormalities

Dr. A. G. BAIKIE (Edinburgh) said that in acute leukæmia in adults, chromosome abnormalities had been found in about a third of the cases studied. These abnormalities included changes in chromosome number and morphology. In no two cases had the same abnormality been demonstrated. The real incidence of chromosomal changes in acute leukæmia might be very much higher than indicated by these results. The results of simultaneous culture of blood and bone-marrow suggested that some negative findings might be due to the failure of leukæmic cells to divide in culture so that they are outgrown by normal cells present in the original sample. In contrast the abnormal chromosome in chronic myeloid leukæmia (the Philadelphia chromosome) was an apparently specific abnormality and may be found in some instances of the disease. The minority of cases of chronic myeloid leukæmia in which the Ph^1 chromosome was not found had yet to be defined, but may include instances of the disease which ran a relatively benign course but were not otherwise atypical. Comparison of the frequency of occurrence of the Ph^1 chromosome in treated and untreated cases suggested that cells carrying the Ph^1 chromosome may be more sensitive to the effects of both X rays and busulphan. Studies of instances of acute leukæmic transformation in chronic myeloid leukæmia showed the frequent emergence at this stage of a second cell line distinguished by an abnormal chromosomal number. It seemed likely that the presence of the Ph^1 chromosome in a cell made that cell especially liable to further genetic change.

Miss KARIN BUCKTON (Edinburgh) described how chromosomes 13 and 14 (and possibly 15, 21, and 22) had satellites which might be associated with nucleolar organisation. Satellites from one chromosome could form an association with one or a number of other satellites. The stickiness of the satellites on the acrocentric chromosomes might make these autosomes prone to divisional errors. Trisomy of chromosomes 13 has been described by Patau et al. Trisomy of chromosomes 21 was associated with mongolism. The formation of the cell with an additional autosome probably occurred through non-disjunction during gametogenesis. Not all mongols had 47 chromosomes. The third chromosome 21 could become translocated on to another chromosome, giving 46 chromosomes. Cases with a translocation between a chromosome 21 and one chromosome in the group 13–15 or another 21 or 22 had been reported. It had been possible, particularly in some families with more than one mongol, to trace the translocated chromosome to one of the parents and other apparently normal sibs in their sibship. Not all children born to a parent who carried the translocated chromosome would be mongols, but the probability was much increased. The demonstration of mongol mosaics was of interest. The distribution of 47 and 46 cells could explain why one case (unpublished) of mongol mosaicism had most of the features of mongolism while another case described by Clarke did not. Mosaicism might be the explanation for some of the unusually intelligent mongols. It was known that mongols had an increased liability to leukæmia and the occurrence of the two conditions in one sibship was known where the mother and at least one of the mongols had a " 15 "/21 translocated chromosome.

Type-81 Staphylococcus in a General Hospital

Prof. C. A. GREEN and Dr. I. A. PORTER (Newcastle upon Tyne) described an antibiotic-resistant strain of *Staphylococcus aureus* responsible for an outbreak of infection involving 61 individuals over a period of fifteen months in the medical and surgical wards of a general hospital. The strain of staphylococcus was lysed by phage 81 only when it was employed at a thousand times its routine test dilution. The transfer of a patient from an infected ward to a previously uninfected ward was an important means of spreading the infection. Skin lesions and infection of surgical wounds were the most common manifestations, but the rarer pulmonary and urinary infections were more dangerous. Investigations in one ward showed that the infected patient and the established nasal carrier of staphylococci were the most important sources of infection. It is believed that this outbreak was brought to an end by isolating infected patients and by certain minor changes in wound-dressing techniques.

Hepatic Cirrhosis and the Thyroid

In view of histological and immunological reports relating thyroiditis to the presence of hepatic cirrhosis, Dr. G. SCLARE, Dr. A. NICOL, and Dr. G. TAYLOR (Manchester) had studied postmortem histological changes in the thyroid in 77 cases of cirrhosis and an equal number of controls matched for age and sex but with no evidence of thyroid or liver disease. Unexpectedly, the results failed to reveal any significant difference between the two groups in the incidence and severity of lymphocytic infiltration of the thyroid. But a high proportion of the thyroid sections in the cirrhotic group showed an increase in fibrous tissue, unrelated to lymphocytic infiltration or to nodule formation. This fibrotic thyroid lesion was present in 23 cases of cirrhosis of the liver as against 8 control cases. The preponderance was greatest in women over 50: of 26 in this group, the lesion was present in 11 cirrhotic cases and in 2 control cases. When the thyroid fibrosis was recorded in three arbitrary grades, it was found that 12 of the cirrhotic cases but none of the control cases fell in the two higher grades. A parallel study of sera from patients with no clinical evidence of thyroid disease included 33 cases of cirrhosis of the liver and 200 control cases. Thyroid-specific (tanned-cell agglutinating) autoantibody was significantly increased in the cirrhotic group; and the increase was greater in females.

Diagnostic Tests for Thyroid Antibodies

Dr. J. R. ANDERSON, Dr. J. S. BECK, Dr. R. B. GOUDIE, and Dr. KATHLEEN G. GRAY (Glasgow) observed that since minor degrees of thyroiditis were common and of no clinical importance, a useful diagnostic test must be relatively insensitive, positive results indicating severe degrees of chronic thyroiditis. Results with precipitin, tanned-red-cell agglutination, and complement-fixation tests showed the precipitin test to be at least as good as the other two for diagnosis. Since the precipitin test was also the simplest, requiring neither inactivation nor titration of the serum, it was preferable. The Ouchterlony method had certain advantages over other precipitin tests, but some sera took several days to give a precipitate. The latex aggregation (" TA ")* test for antithyroglobulin was performed upon 400 sera: with 24, the test disagreed with the precipitin test. This was because (1) occasional Hashimoto sera contained precipitin which did not aggregate sensitised latex (nor agglutinate sensitised tanned red cells); (2) the " TA " test was generally more sensitive than the

* Reagent supplied by Hyland Laboratories, Los Angeles, California.

precipitin test; (3) approximately 2% of control sera gave apparently false positives with the "TA" test, which were not annulled by pretreatment with thyroglobulin. False positives were virtually eliminated by accepting as positive only sera which aggregated latex at both serum concentrations tested (undiluted and 1 in 20). For diagnostic purposes the precipitin test was slightly superior to the "TA" test. No serological diagnostic test detected all cases of Hashimoto's disease, nor did a positive result exclude the possibility of other disorders—e.g., thyroid malignancy accompanying chronic thyroiditis.

Blood-lipids in Myocardial Necrosis

Dr. J. B. ENTICKNAP (London) had examined seven fractions of the blood-lipids in about 800 cadaver sera. All were abnormal in ischæmic heart-disease, and a regular pattern of differences was seen. They were most abnormal when a coronary-arterial thrombus was demonstrated at necropsy but only slightly abnormal when the predominant finding was myocardial necrosis. The lipids in cases with gross myocardial fibrosis were moderately elevated and closely resembled those of arterial disease not affecting the heart. The pattern of coronary occlusion by atheroma without thrombus or necrosis most closely resembled coronary thrombosis. In non-ischæmic heart-disease the lipids resembled those in death from other causes. It thus appeared that onset of myocardial necrosis might be associated with a fall in blood-lipids that were previously elevated. The findings also supported the contention that coronary occlusion might cause death in the absence of demonstrable necrosis or thrombosis. Some data from clinical cases were consistent with these necropsy findings.

Non-specific Jejunitis in Children

Dr. A. H. CAMERON and Dr. K. B. ROGERS (Birmingham) reported that 80 jejunal biopsies at the Birmingham Children's Hospital had revealed a small group of non-specific jejunitis as well as a major group showing a flattened mucosa characteristic of cœliac disease. There was a high prevalence of infestation with *Giardia lamblia* in the group with non-specific jejunitis, and the patients' symptoms responded to treatment with mepacrine. In 3 children with non-specific jejunitis no cause could be found.

Reviews of Books

Smoking

Its Influence on the Individual and its Role in Social Medicine. C. VAN PROOSDIJ, specialist in internal medicine, 'Zonnestraal' Hospital, Hilversum, Netherlands. Amsterdam: Elsevier. 1960. Pp. 319. 57*s.* 6*d.*

IN this comprehensive and well-written account of the tobacco habit, the available evidence about the influence of smoking on the respiratory, cardiovascular, and nervous systems, and on the digestive and sexual organs, is excellently reviewed and impartially analysed. The verdict is that it has now been established that the chances of getting lung cancer increase consistently with the number of cigarettes smoked, that cigarette smoking is probably an ætiological factor in the production of chronic bronchitis, and that smoking has undoubtedly an adverse effect on thromboangiitis obliterans and probably also on gastric ulceration. Judgment on several other counts is reserved until there is further evidence. This section of the book, with its copious bibliography, will be of special value to research-workers and clinicians, but other chapters dealing with the historical, economic, psychological, and preventive aspects of the tobacco problem are equally instructive and offer some fascinating information not readily available elsewhere.

Despite the growing awareness among the general population of the perils of smoking, Dr. van Proosdij thinks it is unrealistic to expect any wide abandonment of the habit in the foreseeable future; for, apart from the ubiquitous propaganda in favour of smoking, he believes that tobacco satisfies a basic human need for relief from the tensions of everyday life, and that so far no other drug is available which is capable of acting as a satisfactory substitute. He thinks that the most hopeful policy is to persuade young people not to acquire the habit, and to try to induce addicts to switch from the pernicious cigarette to the less dangerous pipe or cigar. Instead of exhorting smokers to abstain altogether, it might be more profitable, he suggests, to urge them to moderate their consumption on the grounds that by exercising restraint they will be able all the better to savour the pleasures of the weed; but many will think that there must be a happy medium between this very mild policy and the more headlong measures which, it appears, have been employed against smokers in the past, such as knouting, banishment, and sticking a pipe-stem through their nostrils.

This book is strongly recommended to anyone interested in the tobacco habit: whether he seeks information about the chemical composition of tobacco smoke or the record "juice fling" of a tobacco chewer, he will not be disappointed.

Cirrhosis of the Liver

MARTIN SELER KLECKNER, Jr., A.B., M.S., M.D., assistant clinical professor of medicine (gastroenterology), Vanderbilt University School of Medicine, Nashville, Tennessee. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960. Pp. 729. 196*s.*

EXCELLENT textbooks exist on the liver and its diseases; so the need for a specialised treatise on one type of liver disease, although a very important one, may well be questioned. The author, however, has undoubtedly succeeded in providing a book of much value to clinicians and pathologists faced with the many problems of patients with cirrhosis. As he rightly emphasises, there is confusion in the whole subject of hepatic cirrhosis because its definition lacks precision. The central criterion of true cirrhosis required by the author is nodular regeneration: everything else is of secondary importance.

Within this self-imposed limitation the literature has been meticulously abstracted and, with few exceptions, condensed into a volume remarkably easy to read and superbly illustrated. One exception is the unsatisfactory chapter on experimental cirrhosis, which, Dr. Kleckner says in a preface, "bears little or no relation to the human type".

A valuable feature of almost every section is the many tables clearly presenting the clinical, pathological, and biochemical data, derived from large series of patients, for each type of cirrhosis. The author's own experience is often compared with other large series, thus providing a reliable and convenient picture of the incidence of almost every feature of the disease. Perhaps even more useful is the extensive world-wide bibliography that gives the full title to each reference. There are rather a lot of printing errors, the index might be improved, and the price is steep; but this is still a very useful book.

Experiments In Personality

Vol. I. Psychogenetics and Psychopharmacology. Pp. 262. 40*s.*
Vol. II. Psychodynamics and Psychodiagnostics. Pp. 333. 40*s.*
Editor: H. J. EYSENCK, PH.D., professor of psychology, University of London. London: Routledge & Kegan Paul. 1960.

THESE papers were published as a book in order to preserve the unity of a research programme in progress at the Maudsley Hospital, to enable the eleven contributors to write at the length they preferred, and to mark the tenth anniversary of the founding of the Institute of Psychiatry, including its department of psychology, as part of the University of London.

In the first volume P. L. Broadhurst describes studies of emotional behaviour in rats, and concludes that inappropriate genetical models and methods were often used in the past. He emphasises the greater suitability of the hypothesis of multifactorial or polygenic inheritance in psychology. In a selective breeding experiment for high and low defæcation responses of

rats in the open-field test, the results showed a profound effect of selection upon the level of defæcation and upon sex differences in it, with an ancillary effect on ambulation and body size.

R. A. Willett describes the methods used in the separate studies of the effects of two drugs, glutethimide (' Doriden ') and meprobamate, on a group of 24 adults. Subsequent chapters describe the effects of these depressant drugs on various aspects of human behaviour: on learning and conditioning, on some perceptual processes (H. C. Holland), on vigilance and psychomotor performance (Emer Treadwell), on palmar skin resistance and adaptation (Irene Martin), and on reaction times and " set " (Irene Martin). In a final chapter, H. J. Eysenck and S. B. G. Eysenck apply canonical variate analysis to test certain psychopharmacological hypotheses. The effects on behaviour of meprobamate and glutethimide, a tranquilliser and hypnotic respectively, were identical in the five selected tests. Susceptibility to these drugs appeared to be a constant personality feature, and some correlations of this susceptibility with extroversion and neuroticism were found, although not at a statistically significant level.

Volume II is in three parts. The first, experiments in psychodiagnostics (R. W. Payne and J. H. G. Hewlett), is a study of thought disorders in psychotic patients. Three main aspects of psychotic thought disorder were investigated—retardation, overinclusion, and concreteness. Part two, experiments in psychodynamics, has papers on the excitation-inhibition balance in neurotics (Gordon Claridge) and in normals, learning and conditioning (R. A. Willett), perceptual functions (H. C. Holland), and a factor analysis of selected tests (H. J. Eysenck). Part three, experiments in psychometrics, contains three chapters on statistical method (P. Slater) and an epilogue by the editor on the place of theory in psychology. Eysenck's view is that, although in psychology almost any theory is " weak " compared to the " strong " theories in a science such as physics, a " weak " theory is of great value since it directs attention to those problems that most repay systematic study.

Cancer

Progress Volume 1960. Editor: RONALD W. RAVEN, F.R.C.S., joint lecturer in surgery, Westminster Medical School, University of London, and surgeon, Westminster Hospital Teaching Group, London. London: Butterworths. 1960. Pp. 258. 60*s*.

THIS book appeared two years after the 6-volume system of cancer edited by Mr. Raven; and, though it sets out to show that progress is being made in cancer research throughout the world, many readers will feel that no major contribution has been made during the past few years, and certainly not in the past two. The big advance that is confidently awaited is yet to come.

The progress volume is a series of articles on such topics as skin tumours, smoking and cancer, radiotherapy, chemotherapy, and hormonal therapy. Those which deal fairly fully with recent work are summaries concerning (i) iron dextran as a carcinogen; (ii) industrial cancer of the lungs, nose, and nasal sinuses; (iii) the polyoma virus; and (iv) carcinoid tumours.

The editor's remark that " our first objective is to control cancer ", and that " to achieve this will demand an enormous international effort ", may draw the reply that we already know that lung cancer could be largely controlled in this and other countries if teenagers and other young people could be persuaded never to start smoking cigarettes. It is true that we cannot yet control many other forms of cancer; but what effort is made to control the one preventable type?

Man: the Bridge Between Two Worlds

FRANZ E. WINKLER, M.D. London: Hodder & Stoughton. 1960. Pp. 266. 21*s*.

THE author, Austrian by birth, qualified in Vienna where for a time he practised general medicine; later he emigrated to the United States and has practised in New York, whether as physician or psychiatrist is not quite clear. Psychology interested him from youth and he noted in Vienna the equivocal effects on personality of technically successful analytic psychiatry which might convert " an overconscientious business man into a level headed thief or a neurotic housewife into a contented adulteress ". Thus medical experience set him thinking; but he has drawn his material as much from literature as from life, his outlook is essentially that of a European, and he expresses himself in vivid and idiomatic English.

His thesis is that the world physical and the world spiritual are equally real and valid; Man, compact of both, can perceive both, but modern Western man has almost lost his spiritual sense-organ through disuse and deliberate suppression. We, or our children, could probably regain this perceptive power if we frankly recognised the reality of the " other world " and of our own souls and set about it in earnest, especially by fanning instead of quenching childhood's innate wonder and reverence. We had best be quick before we go spiritually blind for good and find ourselves " gone under " to communism, because, since most of humanity still desires spiritual things, Russia's idealised materialism must prevail over Western ideals caked in unacknowledged materialism.

Some of this, of course, is not new, and it seems possible that Dr. Winkler does not know how many poets—Thomas Traherne, Wordsworth, Whitman, and Francis Thompson, among others—have warned us or shown the way. But the thesis is cogently presented; there is point and pith in almost every paragraph; and he puts " a new slant " on many myths, legends, and historic events. For troubled citizens of a troubled world the book makes good and helpful reading.

Recent Advances in Pathology (7th ed. London: J. & A. Churchill. 1960. Pp. 459. 48*s*.).—This very useful book, now edited by Prof. C. V. Harrison, was first published in 1932 under the joint authorship of Prof. Geoffrey Hadfield and Prof. L. P. Garrod. By 1953 increasing specialisation in pathology persuaded the then editor, Dr. Hadfield, that no single author could do justice to the whole subject, and the help of several contributors was enlisted. The new editor has wisely followed this precedent and has been singularly fortunate in his choice of collaborators and material. Professor Harrison himself has given a valuable account of diseases of lymphoid tissue, the liver, and the arteries. Nuclear sexing is admirably dealt with by Dr. Bernard Lennox, who, in collaboration with Dr. Mary Catto, has also written with great clarity on the histology of some recently recognised tumours. The section on diseases of the lung by Prof. Jethro Gough is distinguished by a detailed account of his technique of paper-mounted sections. Dr. R. H. Heptinstall, on diseases of the kidney, has done much to clarify the morbid anatomy of the nephrotic syndrome. In a commendably brief article Dr. J. Ball has adequately described the two fundamentals of bone pathology, deposition and resorption. The longest and most comprehensive article, that by Prof. I. Doniach on diseases of the endocrine system, is a masterpiece of clarity and condensation. Dr. Georgiana Bonser, with two of her colleagues at Leeds, has summarised the main features of recent cancer research; and the very important current problem of toxic radiation is reviewed by Dr. R. H. Mole of Harwell. This well-produced and liberally illustrated book is commended without reserve to all serious students of pathology and medicine.

Textbook of Medical Physiology (2nd ed. Philadelphia and London: W. B. Saunders. 1961. Pp. 1181. 108*s*.).—The new edition of Prof. Arthur C. Guyton's work has been extensively reorganised. Special emphasis is given to the idea of the body as a single functioning organism integrated by interlocking control systems. To underline this approach, first place is now given to the chapters describing the regulation of the body fluids. The text is much improved both in accuracy and clarity, and the clinical information is as up to date as the physiological—a wonderful achievement in a text written by one man. The book is now probably the best single-author textbook of physiology.

THE LANCET

LONDON 29 APRIL 1961

Neurology in the Tropics

IT has long been recognised that certain specific infective and parasitic disorders which involve the nervous system are seen only in tropical countries. Leprosy, cerebral malaria, and sleeping-sickness are examples. However, recent field studies of the epidemiology of several common neurological diseases such as disseminated sclerosis have revealed striking differences between the prevalence of the condition in countries of temperate climate on the one hand and in the tropics on the other. It is now apparent that disseminated sclerosis is common in temperate areas but very rare in the tropics, and that this difference of prevalence does not depend on race [1]; furthermore, in Japan, classical disseminated sclerosis is also uncommon but the syndrome of neuromyelitis optica or bilateral retrobulbar neuritis is more often seen.[2] Disseminated sclerosis is rare also in South Africa, where, however, porphyria is relatively common.[3] An interesting observation is that the Chamorro peoples who inhabit the islands of the Mariana group in the South Pacific have a remarkably high incidence of an inherited variety of amyotrophic lateral sclerosis, indistinguishable from the sporadic form of the disease as usually seen in Britain and the U.S.A. Indeed in the Mariana islands the disease is one of the commonest causes of death; but the ætiological factors here are clearly genetic and racial rather than climatic, for it is similarly prevalent in Chamorros living in California.[4]

Other obscure neurological disorders to which attention has been paid in recent years, and some of which are seen almost exclusively in tropical countries, are kuru, " tropical amblyopia ", and a form of spastic paraplegia which seems to be particularly common in Jamaica. Kuru [5] is a degenerative disease of the nervous system noted in natives of the eastern highlands of New Guinea. It gives rise to emotional disturbance, widespread tremor, ataxia, parkinsonian features, and progressive dementia and paralysis; it is fatal in six to nine months. Pathological study reveals widespread degenerative changes in the cerebellum and in extrapyramidal neurones. Probably genetic factors are important in the ætiology [6] but the pathogenesis remains obscure. " Tropical amblyopia " appears to be common in the West Indies, and in 1956 DEGAZON [7] was able to review 298 cases seen in Jamaica in eight years. It gives rise to visual failure, pallor of the optic discs, and central or paracentral scotomata, and it closely resembles nutritional amblyopia as seen previously in the Middle East [8] and in prisoners-of-war. Though not all patients with this condition appear to be undernourished, it is probably a deficiency disease whose nature is not yet completely clear.

In a valuable new report CRUICKSHANK, MONTGOMERY, and SPILLANE [9] review 210 cases of spastic paraplegia in Jamaica. Sometimes the onset of the condition was acute, but more often the patients showed spastic weakness in the lower limbs of gradual onset and progression with a tendency to clinical arrest after several months or years; even when the disease seemed arrested, however, most cases were so disabled as to be incapable of working. Loss of vibration and of postural sense in the legs was usual, urinary difficulty was common, evidence of retrobulbar neuritis was found in 25% of cases, and nerve deafness was found in 23%. In 24 cases (11%) there was muscular wasting in the feet and calves and less commonly in the hands, resembling superficially the clinical picture of peroneal muscular atrophy, and indicating involvement of the lower as well as of the upper motor neurones. The blood Wassermann reaction was positive in 35% of cases—a prevalence comparable to that found in the Jamaican population as a whole and usually indicating infection with yaws rather than with syphilis. No consistent hæmatological abnormalities were discovered, though there was histamine-fast achlorhydria in the gastric juice in 31% and the cerebrospinal-fluid protein content was usually raised. Serological tests for syphilis in the fluid were negative. Pathological examination of necropsy material obtained from 2 cases, reported upon by W. H. MCMENEMEY, revealed extensive white-matter degeneration and some nerve-cell involvement in one case, suggesting a toxic or metabolic disorder, while in the second case the appearances were those of a vascular myelopathy with some cellular exudation. Professor CRUICKSHANK and his colleagues agree that their 210 cases may have included disorders of multiple ætiology; they suggest that in most cases circumstantial evidence indicates that the disorder is due to malnutrition in the broadest sense. Possibly the toxic principles present in " bush teas " may play an important part. But conclusive evidence concerning ætiology is lacking and it is clear that these cases would greatly repay further scientific study. Indeed this is one of the many " new " disorders of the nervous system which are being described in increasing number in tropical countries and which seem likely to offer fruitful opportunities for neurological research.

It is to be hoped that the work of the Problem Commission of Tropical Neurology, recently set up by the World Federation of Neurology, will draw attention to some of these fascinating disorders and encourage young neurologists and research-workers to undertake periods of study in some of the countries concerned. Results obtained by the investigation of these obscure neuro-

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logical disorders seen in the tropics may incidentally throw light upon the pathogenesis of some of the so-called incurable diseases of the nervous system, such as disseminated sclerosis, which are so prevalent in more highly industrialised communities.

Porphyria

SINCE GÜNTHER'S [1] original classification of the porphyrias in 1911 into acute, acute toxic, chronic, and congenital types, much has been learnt about the incidence, pathogenesis, and biochemistry of these diseases. In the past, the porphyrins were the esoteric province of a few dedicated chemists and biochemically minded physicians; and the porphyrias were diseases relegated to the small print of the big medical textbooks, achieving a wider fame only through a student limerick. Today the porphyrins and their metal complexes are being studied in many departments of the biological sciences; while the porphyrias, though still generally rare, have become relatively common diseases in some parts of the world.

The remarkable incidence of so-called variegate porphyria among white South Africans of Dutch descent has been traced to an early Dutch settler, who married at the Cape in 1688.[2] DEAN [3] has reckoned that about 10,000 white people of the South African community, including the Rhodesias, have inherited the mendelian dominant gene for this type of porphyria. In affected families the females are usually subject to attacks of variegate porphyria, which resemble those of acute intermittent porphyria; whereas the males have light sensitivity, which in the females may be very slight or absent. In addition to this hereditary type of porphyria in white South Africans, there is a non-hereditary type which occurs among Bantu and is characterised chiefly by light sensitivity. Most of these patients are adult town-dwellers, and the disorder may be related to the hepatotoxic effect of adulterated drinks sold in urban areas. The urine usually contains excessive quantities of porphyrins and occasionally increased amounts of porphobilinogen and δ-aminolævulic acid, but the fæcal porphyrins are not significantly increased.[4]

Since 1956 some 5000 new cases of porphyria have been reported in the south-eastern provinces of Turkey.[5 6] The disease most commonly affects children below the age of 15 years. Clinically the patient presents with photosensitive skin lesions, hyperpigmentation, and hypertrichosis, evidence of hepatic disease, and excessive excretion of uroporphyrin and coproporphyrin in the stool and urine. The distribution of the disease has been clearly linked with the distribution of seed wheat dressed with the fungicide hexachlorobenzene; and the disease has not been detected in regions where hexachlorobenzene was not used as a seed dressing. OCKNER and SCHMID [7] have confirmed the toxic origin of this disease by showing that rats fed for some time with hexachlorobenzene in their diet excrete large amounts of uroporphyrin, coproporphyrin, and eventually porphobilinogen.

The emergence of porphyria in South Africa and Turkey has necessitated reasssessment of the classification. The term " porphyria " itself has in the past been reserved for diseases caused by an " inborn error " of porphyrin metabolism. " Porphyrinuria " was used to describe minor disorders of porphyrin metabolism induced by other diseases or by drugs and chemicals. Bantu porphyria and the Turkish type are both almost certainly caused by intoxicants, and yet they are comparable in clinical severity and in the extent of the porphyrin abnormality with the hereditary type of porphyria cutanea tarda. Furthermore, the main clinical features of these conditions are due to the porphyrin dyscrasia. The place of variegate porphyria in classification also presents difficulties. DEAN and BARNES [8] have found a high fæcal porphyrin in remissions of this disease, with an increase in urinary porphyrins and their precursors during the acute phases. This suggests that variegate porphyria belongs to the group of cutaneous porphyrias in which RIMINGTON has demonstrated reciprocity in the excretion of porphyrins, in contradistinction to acute intermittent porphyria of the Swedish type in which no such increase of fæcal porphyrin was found in remission. On the other hand the clinical pattern of variegate porphyria more readily fits WATSON'S " mixed porphyria ", and WATSON [9] notes that these biochemical differences between acute intermittent and variegate porphyria are indeterminate in the cases found in the United States. He has also found cases of cutaneous porphyria in families in which other members showed the classical pattern of acute intermittent porphyria. In Sweden [10] and Great Britain,[11] by contrast, acute and cutaneous porphyria were apparently never associated with each other in affected families.

WATSON has considered the possible causes of this difference in the U.S.A.—for example, genetic factors due to the " melting-pot " character of the population, or the interplay of environmental or other non-genetic factors on the same underlying genetic defect.

To take account of those problems, WATSON has suggested an extended classification of porphyria.[9] The main subdivisions are into (I) porphyria erythropoietica (congenital porphyria) and (II) porphyria hepatica. Acute intermittent porphyria (IIA), manifest or latent, is a hepatic porphyria, demonstrated by WATSON'S own chemical-pathological studies and by the experimental work of GOLDBERG and RIMINGTON.[12 13] Another form of hepatic porphyria is the hereditary mixed or variegate group (IIB) with various combinations of acute intermittent and cutaneous symptoms. WATSON defines three further types of hepatic porphyria—a hereditary cutaneous type (IIC), a constitutional or idiosyncratic type (IID) in which cutaneous symptoms are brought

1. Günther, H. *Dtsch. Arch. klin. Med.* 1911, **105**, 89.
2. *Lancet*, 1959, ii, 93.
3. Dean, G. *S. Afr. med. J.* 1960, **34**, 745.
4. Eales, L. *S. Afr. J. Lab. clin. Med.* 1960, **6**, 63.
5. Cetingel, C. I., Özen, M. A. *Blood*, 1960, **16**, 1002.
6. Schmid, R. *New Engl. J. Med.* 1960, **263**, 397.
7. Ockner, R. K., Schmid, R. *Nature, Lond.* 1961, **189**, 499.
8. Dean, G., Barnes, H. D. *S. Afr. med. J.* 1959, **33**, 246.
9. Watson, C. J. *New Engl. J. Med.* 1960, **263**, 1205.
10. Waldenström, J. *Amer. J. Med.* 1957, **22**, 758.
11. Goldberg, A. *Quart. J. Med.* 1959, **28**, 183.
12. Goldberg, A., Rimington, C. *Lancet*, 1954, ii, 173.
13. Goldberg, A. *Biochem. J.* 1955, **59**, 37.

about by chemical causes, especially alcohol, systemic disease, or for no known reason; and finally an acquired hepatic porphyria (IIE) caused by a hepatic adenoma [14] or secondary to a chemical such as the fungicide implicated in the widespread Turkish epidemic. This classification does help to clarify the position of the porphyrias in relation to our present knowledge of the clinical and biochemical disturbances. But much further study is needed to establish the exact enzymic sites which are deranged in these diseases, and the relation of these biochemical abnormalities to the clinical manifestations.

Le Fort's Operation

IN this country there is little enthusiasm for LE FORT's operation for prolapse of the uterus. Many gynæcologists regard it as having been long ago supplanted by the Donald-Fothergill, or Manchester, operation. This is unfortunate, for Le Fort's operation still has an important though limited place in the management of severe prolapse in elderly or infirm patients.

In his original article in 1877 LE FORT [15] reviewed the various procedures for correcting uterine prolapse. Common to all was the practice of removing part of the vaginal epithelium and suturing together the partially denuded anterior and posterior vaginal walls. Some techniques were easy but ineffective, while others controlled the prolapse but were very difficult and carried serious risk for the patient. By Le Fort's method, which was suitable for the severest degrees of prolapse, the vagina was converted into two rigid, narrow canals, parallel to one another; a firm median septum between the two canals acted as a support, preventing descent of bladder and rectum. It had the advantage that everything could be done externally with great ease. At the time this was a notable advance in surgical technique, and the value of LE FORT's contribution was generally acknowledged.

Fifty years ago the Manchester colporrhaphy was developed by DONALD[16] and FOTHERGILL.[17–20] By this technique prolapse is corrected without narrowing the vagina; and, with individual modifications, this is now a standard operation throughout the world. But some women are either too old or too ill for colporrhaphy, and some other procedure is necessary. Vaginal rings and cup and stem pessaries have serious disadvantages, especially in elderly patients. If left in position too long they cause ulcerative vaginitis and may, in time, lead to cancer of the vagina: in most gynæcological clinics one or two examples of the " forgotten pessary " are seen each year.[21] A large sponge, with tape attached to facilitate removal, is gentler on the vaginal tissues but does not effectively control severe prolapse. These palliative measures inevitably become a burden to patients and relatives, and have no place in modern gynæcological practice.

14. Tiong Hoo Tio, Leijnse, B., Jarrett, A., Rimington, C. *Clin. Sci.* 1957, **16**, 517.
15. Le Fort, L. *Bull. gén. Thér., Paris*, 1877, **92**, 337.
16. Donald, A. *J. Obstet. Gynæc. Brit. Emp.* 1908, **13**, 195.
17. Fothergill, W. E. *Trans. Edin. obstet. Soc.* 1908, **33**, 129.
18. Fothergill, W. E. *Brit. med. J.* 1913, i, 762.
19. Fothergill, W. E. *Amer. J. Surg.* 1915, **29**, 161.
20. Fothergill, W. E. *J. Obstet. Gynæc. Brit. Emp.* 1921, **28**, 251.
21. Pritchard, J. G. *Lancet*, Jan. 21, 1961, p. 172.

VARTAN [8] asserts that a patient with severe prolapse who is able to be up and about is fit to have a Le Fort operation: if she is bedridden owing to age or infirmity she is unlikely to require treatment for prolapse. In the past ten years VARTAN has performed 21 Le Fort operations on poor-risk patients and has every reason to be satisfied with the results. He emphasises that this is not an alternative to pelvic-floor repair or vaginal hysterectomy, but maintains that it is clearly preferable to ring and Napier pessaries and other vaginal devices.[22 23] VARTAN's operative technique differs in certain details from LE FORT's, but the principles are the same.

For selected patients there are obvious advantages in this simple operation. The anæsthetic requirements are less rigorous than for the Manchester operation, and if necessary local anæsthesia can be used. There is little dissection, opening up of tissue planes is limited, and the bladder is hardly disturbed. When tissue quality is poor, these are important considerations. Patients can be up and about the day after operation—which to the elderly is a great benefit. In longstanding cases of procidentia, when the skin is œdematous and ulcerated, convalescence is likely to be speeded by preoperative treatment. A week's rest in bed, with a 'Vaseline' vaginal pack to reduce the prolapse and 0·5 mg. of stilboestrol daily, will improve the quality of the vaginal epithelium, ease operation, and reduce the risk of postoperative complications.

Few gynæcologists in their training gain personal experience of this operation, and it is doubtful whether many newly qualified doctors have ever heard of it. As VARTAN points out, within a short time we may lose this valuable geriatric operation. He rightly urges all gynæcologists to learn for themselves how simple it is, and how pleased are patients and their doctors with the results.

Annotations

PATIENTS AS CONSUMERS: WANTS AND NEEDS

SOME people prefer not to know what others think of them; but it is certainly useful to have a report on what people think about their doctors and about the health and welfare services.[24] In 1957 P.E.P. invited comments from families with children under 16 living in the Greater London area. Such households represent about 40% of the total.

Compared with some of the other services, the National Health Service comes out rather well. 99% of the families had used it at some time, compared with 84% who had used National Insurance, 74% education, and 25% housing. Moreover, individual parts of the N.H.S. had also been widely used: 99% of the families had consulted the doctor, 95% the dentist, 86% the outpatient department, 82% the inpatient department, and 58% the optician. In addition, 63% had used the welfare clinic, 55% the health visitor, 17% the midwife, and 13% the

22. Vartan, K. *J. Obstet. Gynæc. Brit. Emp.* 1960, **67**, 470
23. Vartan, K. Personal communication.
24. P.E.P. (Political and Economic Planning). Family Needs and the Social Services. London: George Allen & Unwin. 1961. Pp. 233. 30*s*.

home nurse. 92% of the mothers in the sample thought that the health services had been " a real help ". (Only 54% thought this of education, 47% of family allowances, and 17% of housing.) Only 1% of those who had used it had found the health service of insufficient help. 30% of the sample thought that the Government should spend more money on it, and 9% thought they should spend less. The reason why so many thought that more should be spent was not because they thought the health services bad but because " they are so important ", because " doctors and nurses should be paid more ", or because " there shouldn't be charges for treatment ". Doctors came second to relatives, and before friends, in the list of those who had been helpful in times of trouble.

Though appreciaton of the health service was evidently sincere, some aspects of the report are rather disturbing. In families of every type and size, ill health had most often been the chief worry during the previous year. In 39% someone in the family was receiving treatment for some long-standing complaint, and in a further 37% someone in the family was suffering pain or discomfort that was not being treated. These figures are surprisingly high. As many as one family in ten had someone who needed special care in addition to, or apart from, ordinary medical treatment. The proportion of mothers who thought their own health was not too good varied from 11% in the managerial and professional class to 27% in the unskilled operative class. If teeth and eyes are included, the corresponding figures are 25% and 53%. In 20% of the sample, someone in the family had pain or discomfort of the teeth which was not being treated. 60% of the reasons given for this amounted to procrastination, and a further 17% mentioned the difficulty of finding time, which is much the same thing. Money was mentioned by 12% and failure to get an appointment by only 1%. Most people seemed to recognise that it was their own fault when they did not get treatment.

There was greater dissatisfaction with individual aspects of the health services than about these services in general. 13% had some complaint about their last stay in hospital. Although only 4% complained of an inconvenient wait for a hospital outpatient appointment, 22% complained about inconvenient waiting at the outpatient department. 10% had some complaint about the last consultation or some other occasion. Almost every family in the sample had used the general-practitioner service; on the whole mothers were appreciative of the kind of help they got. But even so, there was a good deal of criticism. In 98% of the families in the sample everyone was registered with a general practitioner and 79% of them had everyone registered with the same one. Although 86% were satisfied with the kind of attention given by their present doctor, 27% said that someone in the family had either changed or wished to change, through dissatisfaction. In 15% a change had actually taken place. 14% of the mothers were not always satisfied with the attention given by the present doctor; 12% complained either about what happened at the last consultation or about some other occasion; and 15% expressed dissatisfaction with treatment being received for some long-standing trouble. The most serious complaint, as judged by the worry it caused, was that the doctor delayed visiting the home; but many of the complaints about treatment showed that the mother lacked confidence in the doctor. When the mothers were particularly happy about the service from their doctor it was often because they felt he was friendly, ready to examine, and ready to listen and to take an interest in them or their children. They were much more likely to feel this about the welfare clinic and did not always expect it from the general practitioner. Though some criticism came from families of all types and sizes, it was greatest from the middle classes. There had been rather more changing from one doctor to another among families at the top than at the bottom of the social scale.

The evidence of this report suggests that the ancillary and welfare services are on the whole much less satisfactory than the main medical services. Of late years there has been a good deal of talk about the need to develop these domiciliary and welfare services so as to help patients who might otherwise have to be in hospital, and also to aid their families. Yet the number of families who had had help from welfare services, other than the welfare clinic and the health visitor, was small—so small indeed as to suggest that these services, on their present scale, cannot be nearly sufficient. 38% of those who had used the home-help service thought it not helpful enough, while 67% of those who felt they needed it had failed to get it. Among those who had used the service, the rate of criticism was high, with 21 out of 55 making a complaint of some kind. As the decision on whether a patient can be nursed at home often depends on whether home help is adequate, the arrangements so far made should certainly have further thought.

The report itself can be criticised, however, for its use of the word " needs ", which usually seems to mean " what mothers said they would like to have ". In Britain the needs created by hunger and poverty no longer have the same meaning as they did even twenty-five years ago: nowadays needs are more often discussed in terms of love, security, gratification, and realisation of desires. The distinction between what is really needed and what is only wanted is no longer clear.

Emphasising the " consumer point of view " can be very valuable because undoubtedly patients have suffered in the past from having no means of judging the medical services and little or no redress against them. But it is well to remember that the " satisfied " patient has not always had the best treatment, and that although most doctors like to satisfy their patients, the ones who do this most effectively are not necessarily the best doctors. It is only through health education in its widest sense that we can ensure that as far as possible our patients' " needs ", in the sense of what they think they would like to have, coincide with good medicine.

THE NUMBERING OF CHROMOSOMES

Dr. Patau's article on p. 933 raises an issue which has been a little too much glossed over in recent writing on the chromosomes of man. The Denver system of chromosomal nomenclature [1] is a notable piece of work, and a triumph of international cooperation; but its indiscriminate use leaves an impression that individual chromosomes can be identified with more certainty than is in fact possible at present. Every analysed mitotic figure that has appeared in the pages of this journal since publication of the Denver report has had every one of its chromosomes paired off and numbered. Yet few of the authors would probably now be prepared to defend the literal accuracy of all these identifications. Every chromosome is in its right group—that one can certainly allow.

1. *Lancet*, 1960, i, 1063.

Beyond this, pairs 1, 2, 3, and 16, and the Y, can be accepted as exactly identifiable; and perhaps pairs 6, 17, and 18 and one or two others; but no more. The whole 6–12 group (including the X) is full of pitfalls to any who attempt to recognise the separate pairs. Even the satellites have proved disappointing as labels.[2] Dr. Patau's statistical analysis [3] of chromosome lengths, which showed among other things the futility of attempting to pair off chromosomes when the standard deviation of the length of each chromosome was larger than the difference in mean size of adjacent pairs, does not seem to have been challenged. The Denver report itself, to anyone who has studied its tables in detail, is full of contradictions when one gets down to figures for individual chromosome pairs.

All this is very true. Yet it is to be hoped that too grave a view of the objections will not be taken; for there is the germ here of the kind of sterile nomenclatural controversy that has bedevilled many subjects in the past. Since the Denver system is the best we have, we should probably be wise to stick to it. Dr. Patau's suggestion, for instance, that the groups be labelled A, B, C, &c., instead of the Denver system's rather clumsy 1–3, 4–5, 6–12, &c., looks well at first sight; but unfortunately such a system is already well established in this country—with the lettering in exact reverse of that proposed by Dr. Patau. (Shades of Moss and Jansky!) Trivial names for the groups may be a laboratory convenience, but for publication the accepted nomenclature should be adhered to.

So far as this journal is concerned, we shall continue to ask contributors to use the Denver nomenclature until an authoritative alternative emerges. Perhaps Dr. Patau would be satisfied if authors in general showed less reluctance to admit their inability to distinguish, say, pairs 9, 10, and 11 from each other.

OVULATION

OVULATION in the human commonly occurs about fourteen days before the onset of menstruation. One method is claimed to recognise ovulation immediately it happens. When active ions (chiefly sodium) transfer across a mucous membrane, minute electro-potentials are produced; and such changes in the vagina can be recorded by means of electrovaginography, in which the apparatus consists of two calomel half-cells connected to pubic and vaginal electrodes. Parsons et al.[4] took daily basal recordings from different patients during menstrual cycles, and found that the patterns were specific and constant for each patient.

From the resultant charts, Parsons claims to identify the timing of ovulation from a +12 to +22 millivolt plateau which is maintained for 24–48 hours. Charts completed for a full menstrual cycle show changing electro-potentials during the menstrual, preovulatory, ovulatory, post-ovulatory, and premenstrual phases. The ovarian hormones produced in differing concentrations during the various stages of the cycle are believed to be the main influences on the potentials produced across the vaginal mucosa. No cyclical patterns were found in patients after a natural menopause, though the flat curve might appear in the negative or positive potential ranges. After wedge resection of polycystic ovaries, the flat curves were replaced by typical cyclical variations in 25 out of 27 patients.

Investigating 50 infertile patients, Parsons showed that 35 ovulated 4–7 days earlier than they had been led to expect. (Unfortunately, he does not state by what method the ovulation had been erroneously determined.) 3 patients were found to ovulate on the 10th day of a normal 28-day menstrual cycle; and, although all had been infertile for a long time, these 3 patients conceived shortly after beginning to practise coitus on the 10th day. Overall, of 123 patients complaining of infertility, 40% became pregnant, 30% did not become pregnant, and 30% had proven pelvic inflammatory disease or partners with oligospermia.

Estimation of ovulation-time by means of basal temperature charts was introduced by van de Velde as early as 1904.[5] Each morning soon after waking the patient takes her temperature and records it on a simple graph. Benjamin [6] has studied 2000 charts from 900 patients, and has shown that 98% had no difficulty in completing the graphs. A slight fall in temperature about the time of ovulation is followed by a 0·2–0·4°F rise which persists during the remainder of the cycle. Thus over the whole of a cycle the chart is typically biphasic. But some dispute that the temperature drop coincides with ovulation. Whitelaw,[7] who performed laparotomies on the day the temperature changes were noted, showed that the graafian follicle might have ruptured up to 72 hours previously. Possibly the temperature change corresponds in time with the death of the unfertilised ovum. Jeffcoate [8] and Benjamin [6] have emphasised the value of basal temperature recordings in the diagnosis of endometriosis—a disorder commonly associated with infertility. Often patients with this disorder have low-grade pyrexia during the menses.

In the latter part of the menstrual cycle endometrial biopsy, cervical-mucus patterns, genital-tract cell smears, and urinary-hormone estimations provide evidence on whether ovulation has occurred in that particular cycle.

Unfortunately for the patient complaining of infertility, the unfertilised ovum lives no longer than 72 hours, and many postovulatory tests become positive much too late in the menstrual cycle to be of immediate value. Parsons' or other methods immediately indicating ovulation seem likely to prove valuable.

DIAGNOSIS OF DIARRHŒA DUE TO ESCHERICHIA COLI

THE fluorescent-antibody technique has now been applied to many immunological problems; but until lately it was hard to use because it involved the preparation of fluorescein isocyanate, which had to be made in the laboratory before it could be coupled to the antibody. Chadwick and his coworkers [9] in Aberdeen evolved an alternative technique which was more simple to apply, but now that fluorescein isothiocyanate is commercially available even the technique using fluorescein is much less difficult than hitherto. In short, the method is now worth considering as a routine diagnostic procedure and not merely as a research tool. The technique has been applied quite widely to diagnostic bacteriology, especially

2. Ferguson-Smith, M. A., Handmaker, S. D. *ibid.* March 25, 1961, p. 638.
3. Patau, K. *Amer. J. hum. Genet.* 1960, **12**, 250.
4. Parsons, L., Whittaker, J. O., Lemon, H. M. *Amer. J. Obstet. Gynec.* 1960, **79**, 736.
5. van de Velde, T. H. Ideal Marriage, London, 1926.
6. Benjamin, F. *J. Obstet. Gynæc. Brit. Emp.* 1960, **67**, 177.
7. Whitelaw, M. J. *Fertil. Steril.* 1952, **3**, 230.
8. Jeffcoate, T. N. A. *J. Obstet. Gynæc. Brit. Emp.* 1947, **54**, 858.
9. Chadwick, C. S., McEntegart, M. G., Nairn, R. C. *Lancet*, 1958, i, 412

in the United States, where a useful account of this aspect of fluorescent-antibody work has recently appeared.[10]

The less easily recognised or less commonly encountered bacteria may often be rapidly and fairly easily identified by fluorescent antibodies; but this technique has now also been studied in the identification of more common organisms—amongst them enteropathogenic strains of *Escherichia coli*. Nelson et al.[11] investigated the use of fluorescein-labelled type-specific antisera to 10 known serotypes of *Esch. coli* in the diagnosis of diarrhœa in children. The labelling of antisera required about 7 days and the use of a cold-room was necessary. Before use, the sera were checked for cross-agglutination against a wide range of organisms including many gut commensals and pathogens. Two rectal swabs were taken from children with diarrhœa—one for culture and the other for examination by the fluorescent-antibody technique. A smear was made from the second swab; after fixation it was stained with a drop of labelled antibody for 30 minutes and then examined by ultraviolet microscopy. Smears were screened with pooled sera; specimens which gave a positive reaction were re-examined with antisera to single serotypes. The fluorescent-antibody staining technique was found to be rather more reliable than the cultural methods.

The more conventional laboratory methods of diagnosing gastroenteritis due to *Esch. coli* have recently been described in an authoritative review by Rogers and Taylor,[12] one of the valuable series on diagnostic bacteriology published by the World Health Organisation. They deal not only with bacteriological diagnosis but also with the management and prevention of an epidemic of *Esch. coli* gastroenteritis. As the antibiotic sensitivity of strains causing gastroenteritis must be determined, cultural methods are clearly essential. But it may well be that when babies admitted to a hospital or nursery are to be examined for specific *Esch. coli* serotypes before admission to open wards, as recommended by Rogers and Taylor, the fluorescent-antibody technique would save time and would also make the examination of several stools (in order to detect intermittent excretors) relatively simple. This technique could also be used to screen hospital staff for carriers—a problem which Rogers and Taylor recognise as much in need of thorough investigation. There is no doubt that this and other applications of the fluorescent-antibody technique in diagnostic bacteriology need assessment in a busy routine laboratory before their value and place can be determined.

LEUCOTOMY REVIEWED

It is now twenty-five years since Moniz and Lima introduced prefrontal leucotomy in the treatment of mental disease. Tooth and Newton's Ministry of Health report[13] just published surveys some 10,365 patients who underwent the operation or its modifications during the years 1942–54. This is in no sense a detailed personal follow-up, but the report does, in the words of the preface by the Ministry's chief medical officer, " convey a general idea of what has happened to these patients ". 41% of all those operated on were regarded as total or social recoveries or as greatly improved at the time of assessment. 13% were classified as " family invalid and social improvement ", and 15% as " family burden and social defect ". Results were better for affective disorders than for schizophrenia. 25% of patients were unchanged, 2% were worse and 4% were dead, death being wholly or partly attributable to the operation. One of the hoped-for advantages of operation was that its effects would be permanent, but 21% relapsed after operation.

Though the selection of patients suitable for leucotomy has improved greatly since 1942, and present results are likely to be better than earlier ones, the operation is much less widely used than it was. Over 1000 patients were operated on each year between 1948 and 1954, but the figure had fallen to 400 or less by 1959. This decrease is due in part to the increasing range and use of drugs in psychiatry; but, as Tooth and Newton suggest, the figures also reflect uneasiness about the operation itself. It seems fairly certain that the brain mechanisms with which leucotomy interferes are in part just those which are important for behavioural flexibility and adaptation; so that even when prominent symptoms are removed the power of adjusting to the varying demands of life is also reduced. This disadvantage is certainly illustrated in the many detailed studies of leucotomised patients that have been made. Those most intimately concerned almost always noticed a loss of the finer nuances of personality: and the higher the emotional and intellectual milieu from which they come, the more the loss is noted. Indeed it is this change that promoted the search for modified leucotomy—for operations which will reduce symptoms but not the stature of the patient's personality. More refined electrolytic lesions, combined with increased knowledge of localisation of cerebral function, may offer new possibilities for the surgical treatment of mental disease. For the next few years, however, drug treatment, backed by advances in cerebral cytochemistry, seems likely to reduce further the number of patients operated upon. Nevertheless, considering the hopeless future that faced many of the patients before the operation, the results of this survey do much to justify the risks that were taken and the time and effort expended on psychosurgery.

The changes in the operation have been either towards cutting smaller amounts of white matter or removing some special region of frontal cortex and its connections on the grounds that they subserved a particular mental function whose reduction would be beneficial. It is generally true that the smaller the operation the less the blunting of personality, but the less the amelioration of symptoms. Lewin[14] has studied the results of two limited operations—orbital leucotomy and cingulectomy. In the affective disorders and neuroses some 50% were greatly improved by orbital operations: and rather fewer (11 out of 26) by cingulectomy. There is a suggestion that cingulectomy has less effect on the higher levels of personality and is therefore best used in those whose way of life demands the preservation of such traits. This new paper of Lewin's, and many others, make it hard to resist the conclusion that the quantity of frontal tissue put out of action is what determines therapeutic success and personality change. Evidence suggesting that small well-defined frontal areas have specific functions is very slight; but this finding does in fact lend support to the efforts to plan the minimum effective operation.

10. Fluorescent Antibody Techniques in the Diagnosis of Communicable Diseases. U.S. Public Health Service Publication 729. 1960. U.S. Government Printing Office, Washington, D.C.
11. Nelson, J. O., Whitaker, J. A. *J. Pediat.* 1960, **57**, 684.
12. Rogers, K. B., Taylor, J. *Bull. Wld Hlth Org.* 1961, **24**, 59.
13. Tooth, G. C., Newton, M. P. Leucotomy in England and Wales 1942–1954. *Rep. publ. Hlth med. Subj., Lond.* 1961, no. 104. H.M. Stationery Office. Pp. 36. 2*s*. 6*d*.
14. Lewin, W. *J. Neurol. Neurosurg. Psychiat.* 1961, **24**, 37.

Needs and Beds

SIDE-EFFECTS OF COMMUNITY CARE

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THIS paper is prompted by a year's experience of running a psychiatric unit in a general hospital. It is not a scientific paper; it reports no original research; it does not contain any scientific data. It is a personal statement based on impressions gained in a new milieu.

Leaving the comparative safety of a large mental hospital, I found myself in close juxtaposition both with general practitioners and with hospital consultants, a state of affairs which notably increases the sense of personal responsibility for one's discipline and one's results. Responsibility is further sharpened in community practice by meeting patients and their families in a more intense and direct way than in the large mental hospital where the anonymity of the great institution tends to blur personal concern.

Community care, like tranquillisers, is a currently popular method of treatment—just as physical methods of treatment were the popular method in the 1940s and " no restraint " in the latter half of the 19th century. As we all know, in medicine new remedies and methods of treatment pass through well-defined stages. At first there are enthusiastic and glowing reports of their efficiency; a little later a few more sober and carefully thought-out reports indicate that this is not the marvellous nostrum that it was originally reported to be; a little later some even more sceptical papers report unpleasant, annoying, and even dangerous side-effects; in some unfortunate examples, one or two fatalities are reported; and in the end its fundamental worth is questioned and it is relegated to a position of minor importance or sometimes given up altogether.

Let me say at once that I believe in community care, as must anyone who has seen the dehumanising effects of long sojourn in the back wards of a large institution, and my only reason for drawing attention to its side-effects is to try to limit them so that the remedy does not fall into disrepute.

BIGGER OUTPATIENTS LISTS

If people are not to be cared for as inpatients, they are to be cared for as outpatients, so there is a bigger load at the outpatient dispensary. It is by no means uncommon for a psychiatrist at one session to see 4 new patients and 8, 9, or even more follow-ups, so the session often extends $1^1/_2$–$2^1/_2$ hours over its time-limit. Even so, the work is rushed, and rushed work nearly always leads to deterioration in quality.

Historically our specialty was the one that had time to offer. Sheer time is perhaps the most valuable commodity the psychiatrist can offer the patient, because clearly it takes time to assess the ramifications of personality. Professor Roth used to say to his students " Don't just do something, stand there ". In a rushed clinic work has to be superficial and nothing annoys a general practitioner more than to get a report which consists of a list of symptoms of which the patient was complaining, ending with a prescription for some drug. The best type of general practitioner regards this as something of an insult because he is fully abreast of modern trends in prescribing, and this is not the management of the case he had in mind when he sent the patient to the psychiatric clinic. In the end the patient simply drifts back to the general practitioner's surgery and nothing worth while has been achieved. Cases which could be carried as outpatients often are sacrificed because their claim on the psychiatrist's time is reduced by the number of people competing for it, and often, in the end, they have to be brought into hospital for reasons other than their intrinsic need. A busy outpatient clinic is often said to save hospital inpatient time; but I wonder if it is really a saving; for admissions still seem to be rising in most places.

Arguing analogously let me draw attention to an article in last July's issue of *Encounter* in which Kingsley Amis replied to the demand in this country for more university graduates to keep pace with the output of American and Russian universities. But, says Amis, university graduates are like poems, or bottles of hock, and not like motor-cars or tins of salmon, in that you cannot decide to have more good ones, all you can decide to have is more, and more will mean worse. The analogy with psychiatric treatment is obvious; the more cases that are treated past a certain optimum point, the worse the treatment will be.

INPATIENT TURNOVER

The psychobiologists and followers of Adolf Meyer have long maintained that much psychiatric illness is the outcome of a particular way of life, and it seems to me that the learning theory of psychology offers incontrovertible support to their hypothesis. If some psychiatric illness is a learned way of life, then by definition learning takes time, and time has been needed for the development of the illness and the pre-illness attitudes of mind and ways of reacting. Equally, time is needed to unlearn these unhealthy ways of reacting, these prejudices in emotional matters, these false physiological suppositions. There has been a tendency lately to be paralysed by statistics, to be hypnotised by the effect of turnover of patients and turnover of beds. We have been warned against the dangers of institutional neurosis,[1] and it is a real danger and needs to be borne in mind; but we ought not to be deceived into thinking that a very quick turnover of patients is necessarily virtuous.

In community care there is a tendency to join in the race to see who can admit fewer patients and discharge them more quickly, but what do the patients themselves (the most important people in the hospital, as we are never tired of saying) think about it? None of them see a doctor for as long as they feel they would like. The plea for more time is strengthened by the fact that the increase in psychiatric referrals from other departments seems often to stem from the rush and bustle which exists there too. Pinsent [2] pointed out that in a general practice, by spending 45 minutes discussing the patient's symptoms and their significance, and then refusing (for reasons which he explained to the patient) to give any medication, he saved 7–8 return visits from the patient for repeat prescriptions. Time spent as an inpatient has an educational value which should not be underrated. If in the past patients were kept too long in hospital, it would be foolish to overcompensate and fall into the error of not keeping them there long enough.

"PSYCHOLOGICAL OVERLAY"

Since I left the mental hospital and began to live in the open market, as it were, with orthopædic surgeons,

1. Barton, R. Institutional Neurosis. Bristol, 1959.
2. Pinsent, R. J. F. H. *Brit. med. J.* 1951, ii, 1335.

general physicians, neurosurgeons, dermatologists, and so on, I have noticed how often difficult cases of asthma, persistent skin rashes, functional dyspepsias, and the after-effects of bone and joint trauma are referred to the psychiatrist. Our colleagues tend to treat a case to the best of their ability, and then, when the patient obstinately refuses to get well, they write on the case-notes that there is a psychological overlay and refer the case to psychiatrists because they are so accessible. With respectable clinics in respectable hospitals, patients no longer resent it, as they might if they were asked to go to a mental hospital. As a result our clinics tend to become the rag-bag and a dumping-ground for failures in other branches of medicine. In itself this does not dismay me, and perhaps half such cases are rewarding to treat; but they are all time-consuming. A few E.C.T.s or a handful of pills do not meet their needs; they are the patients on whom one should spend endless hours explaining mechanisms and restoring confidence, and again the net effect is to load the psychiatrist with more work than he can well undertake.

THE UNSHELTERED PATIENT

The chronic or partially remitted schizophrenic has now reappeared in the community; and though he can live in the sheltered conditions of home up to a point, he cannot hold even a simple routine job. Many of these people are perfectly well and are socially adjusted in an asylum (and I use that old word " asylum " advisedly because it is good to remember that an asylum is a safe place, a refuge from the keen competitiveness and responsibilities of everyday life). They can live comfortably and without distress in an institution; but as soon as they come outside the institution, missing its supports and disciplines, they become social deviants. The recurrent manic can be extremely destructive of familial stability and happiness, especially if she is the mother. The inadequate psychopath can get through the leisurely working day of the hospital without distress but cannot stand up to an eight-hour working day. The youth with schizophrenia simplex can dream his days away in hospital without offending the nurses unduly, but he effectively resists all attempts of psychiatrists, social workers, and disablement resettlement officers to float him off into a useful way of life at home.

These people used to stay in hospital, and, apart from causing a regret to some sensitive and frustrated psychiatrist and some sadness to their families, they did not impinge on the community. Now they are a time-absorbing and often abortive slice of our everyday work. Case conferences discuss them endlessly; social workers support them; they are regular attenders at outpatient departments and as day patients. There is a constant stream of correspondence between disablement resettlement officers and the psychiatric clinic. There are telephone calls from their general practitioners about the difficulties they are causing at home, and so on. It is hoped that the local-authority hostels will take them over one day, as indeed they well might; but at present hostels do not exist at all or are too small to deal with the problem, and there is little promise of their development at least within the next few years; so we in the periphery must continue to carry these patients. They are subtly destructive of morale in the clinic and in the unit, and they steal a large part of every working day—much more than they used to do when they were living out their lives in hospital.

CONCLUSION

All these considerations point inexorably to the psychiatrist's increased case-load. It seems to me that the time has now come when it should be publicly stated what size of population a psychiatrist can reasonably look after. General practitioners, for example, settle for 3500; and this is a maximum figure not an average one. At a recent meeting of the National Association of Mental Health the internationally agreed figure for the population which one psychiatrist could well look after was given as 20,000. On that basis we need eleven more psychiatrists in my hospital group alone. The great populariser of community care in this country was Querido [3] (pace Arthur Pool of Oldham who did not get his recognition until later) and some of Querido's figures can bear repetition:

> For example, Amsterdam is a city of some 850,000 people for which he had 50 psychiatrists. There were 300 inpatient beds, 2 large outpatient departments, 20 policlinics, 2 centres for psychotherapy, and 3 child-guidance clinics. The city is divided into a number of sectors; for each sector a psychiatrist is responsible, together with two or three social workers. The total load of cases for each team is about 400.

Most of us would dearly love to have these resources at our disposal. Here in Manchester we average 1 psychiatrist to a quarter of a million people. If the Government wish community care to succeed, they will have to provide the resources for such a service. Community care is already showing the need for more psychiatrists and more psychiatric time. It seems to me that the present swamping of psychiatric clinics with patients also shows the patients' need for more explanation of their symptoms, of their illnesses, and of the correct attitude to develop towards oneself in matters of health. In the present crowded conditions there is a danger of lowering the quality of service and there is a need for psychiatry to keep up its standards. We are fashionable at the moment, but fashions notoriously change. It is one thing if tuberculosis officers gradually disappear because the disease which brought them into being is disappearing. It is another thing if a specialty wastes away because it has nothing to offer. To be viable psychiatry must not only give a service, it must also teach and it must do some research; but current conditions in community-care practice often barely give a service, and teaching and research are undreamed-of luxuries.

Under the Mental Health Act community care is going to be tried extensively in the next ten years, and society will in the end decide whether it is a success or a failure. Unless we are given reasonable numbers of personnel to carry out the services demanded by the Act, we are in grave danger of jeopardising our specialty.

" . . . One medical superintendent once said, ' Do something new every three months! It doesn't matter what you do, but do something new and keep them thinking!' The method was authoritarian, but the idea valuable; there should always be new moves and developments afoot within the community so that it does not sink, as any group working with long stay disorders may, into dull dreariness. . . The administrative therapist's task is not to be a creator but a selector, seeing which projects are to be encouraged and given scope and which deferred; he acts like a telephone operator, selecting those communications which are of immeditate value and passing them through, choosing which are to wait for a time and which should be ignored."—Dr. D. H. CLARK, *Amer. J. Psychiat.* 1960, **117,** 506.

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Special Articles

CHROMOSOME IDENTIFICATION AND THE DENVER REPORT

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I

NO-ONE will deny that the " Denver Study Group " has succeeded in bringing a degree of order into the nomenclature of human chromosomes. Unfortunately, the Denver report (1960) reflects not only a sensible consensus on nomenclature as a matter of convenience but also an amiable rather than critical attitude of compromise toward contradictory data. The report with its system of chromosome classification has been published and republished extensively, and if the term " standard " implied nothing but wide acceptance the Denver system would qualify. However, the term implies more—at the very least clarity as to what is defined and what is not. The statements: " in those cases where distinction is at present doubtful, final definition of each chromosome can be left until further knowledge has accrued . . ." and immediately preceding: " it is hoped that the assignment of numbers will be permanently fixed " remind one of a blue and a red filter which, when combined, result in opacity.

The Denver Study Group did come forward with some sound proposals. First, it agreed to distinguish seven chromosome groups. Patau (1960), guided by karyograms, suggested independently the same system of groups (cf. also Patau 1961). Secondly, the groups were to be placed " as nearly as possible in descending order of size ". So were, " for the most part ", the chromosomes within the groups. The autosomes were to be serially numbered in this order.

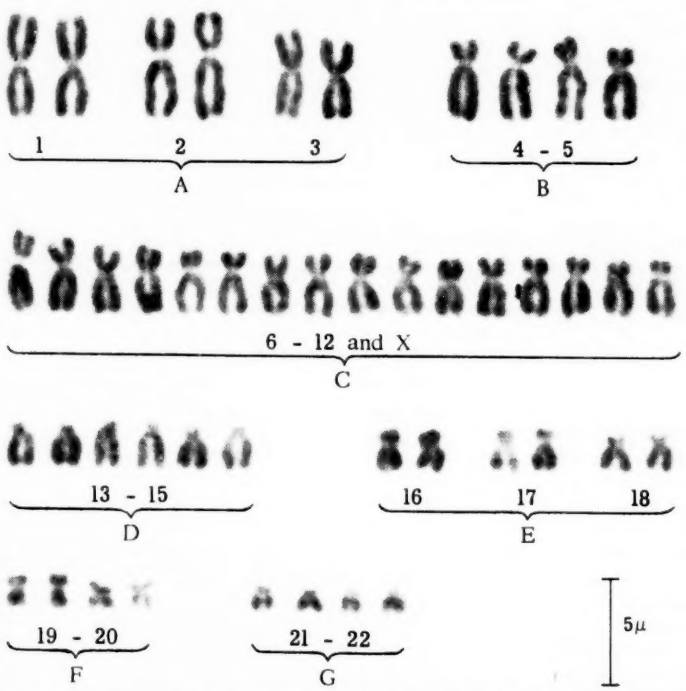
In this system there are two groups, 1–3 and 16–18, in which every chromosome can be identified unequivocally. Two more groups, 4–5 and 19–20, contain two very similar pairs each. It is rarely possible to pair off homologues within these last two groups with any assurance; but when it can be done the numbering will be unequivocal, the larger chromosomes obtaining the smaller number. As far as the definition of the seven groups and the assignment of numbers (following Böök, Fraccaro, and Lindsten 1959) to the above ten chromosomes go, the Denver system is unambiguous and deserves general acceptance.

II

Group 6–12, which includes also the X chromosome or chromosomes, has been discussed at length by Patau (1960) who questioned the possibility of identifying any of these chromosomes with the available techniques. In the present context this is irrelevant; what matters is that the Denver report does not define the individual chromosomes of this group. It is true, " the diagnostic characters " of these chromosomes, based on measurements by six groups of authors, are given in table II. There we learn that chromosome 6 is considerably longer than, about as long as, or considerably shorter than the so-called X, that the latter has an arm ratio of 1·6, 1·7, 1·9, 2·2, or 2·8—all depending on which of the columns of table II the reader chooses to consult. And so it continues. No attempt is made to resolve the discrepancies except by remarking that " many of [them] . . . are due to the measurement of chromosomes at different stages of mitosis and to the effect of different methods of pretreatment and preparation . . ." . One looks in vain for an explanation why these factors failed to affect the measurements by the same contributors of the chromosomes 1, 2, and 3, for which the arm ratios 1·1, 1·5–1·6, and 1·2 respectively, were found consistently. But then, these chromosomes can be identified unequivocally.

No matter what one thinks of the possibility of pairing homologues within group 6–12 and of identifying the X, the Denver report has evidently not defined any one of them. None the less, the reader is advised to arrange the chromosomes " in numerical order, with the sex chromosomes near to but separated from the autosomes they resemble ". Which numerical order?

For most of the individual acrocentric chromosomes that compose the remaining two groups, 13–15 and 21–22 (which also contains the Y chromosome), explicit definitions are given in the Denver report: to wit, chromosomes 13 and 14



Female karyotype (skin tissue culture). Numbers ascribed only to chromosomes that can be identified in almost any technically satisfactory mitosis.

Unequivocal distinction sometimes also possible between 21 and 22 (smaller and with very small short arm) and very rarely between 4 and 5 (smaller) and 19 and 20 (smaller).

Classification (Patau 1960) identical with Denver system in regard to numbers assigned to groups and to such individual chromosomes as are meaningfully defined in the Denver report.

have on their short arms a prominent and a small satellite, respectively, whereas " no satellites have been detected on chromosome 15 "; chromosome 21 has a satellite on its short arm. Table II adds nothing to these definitions of the acrocentric autosomes; in fact, the data are so contradictory (cf. Therman, Patau, Smith, and DeMars 1961) as to invite the conclusion that either the definitions were biologically meaningless or at least part of the measurements were too inaccurate to be relevant. However, when it comes to the Y chromosome the contributors do agree that it has the largest arm ratio in its group, ranging from 2·9 to ∞, but the pleasure of finding for once unanimity fades when one realises that this does not extend to the size of the Y relative to the other members of its group: it is, depending on one's choice of column in table II, the largest or the smallest. Unfortunately, the above definitions by satellite become biologically meaningless once it is granted, as it must be, that all acrocentric chromosomes might have satellites. It is now becoming clear that this is the case. Penrose, Ellis, and Delhanty (1960) mentioned " recent findings of many workers [that] suggest that both chromosomes 21 and 22 may be satellited ". They definitely are (unpublished observations on the chromosomes of several unrelated persons). There is increasing evidence that the same is also true for all chromosomes 13–15 (Therman et al. 1961 and unpublished observations).

If the Denver Study Group has failed to come up with biologically meaningful definitions of the individual chromosomes of group 6–12 and 13–15 it is, in my opinion, because no such definitions are at present possible. It will be shown elsewhere that there is now an exception to this—namely, an autosome of group 6–12 that can sometimes be distinguished by a characteristic secondary constriction. This constriction seems to manifest itself only in blood-culture mitoses, and none too regularly at that. In regard to the small acrocentric chromosomes the Denver report falls short of the possible, as in very favourable mitoses both pairs of autosomes can be distinguished quite well by their size difference (for a discussion of the Y see Patau 1960). In keeping with the general principle of numbering chromosomes as laid down in the Denver report, the larger of the two pairs should be called " 21 ". In my experience, the satellite of 21 is seen less frequently than that of 22. It need not be spelt out where that leaves the identification of the mongolism chromosome.

III

The classification of human chromosomes proposed independently by Patau (1960) differs from the Denver system only as follows: (1) no attempt is made to assign numbers to the individual chromosomes of groups 6–12 and 13–15; (2) the chromosomes 21 and 22 are defined by size, 21 being larger; and (3) the seven groups are given the symbols A through G (see fig.). I would like to go along with any convention that is compatible with the facts and at the same time practical, but I cannot follow the Denver Study Group when they decline to use group symbols, giving reasons which, frankly, I fail to understand. It seems inconvenient to speak of " trisomy for a chromosome of group 13–15 " when " trisomy " for a D chromosome " or, still shorter, " D trisomy " will do as well. Furthermore, group symbols are needed to designate in figures those chromosomes for which no meaningful definition exists or which cannot be identified reliably in the given cell.

The lack of group symbols in the Denver system and, above all, such phrases in the Denver report as " it is believed that with very favourable preparations, distinctions can be made between most, if not all, chromosomes " or " . . . the uncertainty of discrimination at that time " (referring to Ford, Jacobs, and Lajtha, 1958, who very sensibly did not define individual C chromosomes) have apparently combined to induce most workers in the field to publish karyotypes in which every chromosome is given a number—after all, who wants to confess that he has no " very favourable preparations "? The whole thing seems to be a kind of " newspeak ". Ordinarily, the unqualified use of a number such as a " nine " in a scientific illustration would imply that the number has a definite meaning and that it is reasonably certain the number applies in the given case. Not necessarily so in human cytogenetics. The number may simply be the author's way of saying " the chromosome labelled 'nine' *could* be homologous to others equally labelled ". Authors who seriously believe that they can identify C chromosomes such as the X may come up with the claim of having found a C trisomic although the circumstances strongly suggest that it is nothing but a triple-X case.

There are probably quite a few cytologists who would agree that much of the numbering of chromosomes that goes on has no particular meaning, but who also feel that by and large no particular harm is being done either. Maybe so; but what is going to happen when an unambiguous definition of the one or the other chromosome becomes possible? Are future students to memorise the date at which a number that had been used haphazardly before acquired a definite meaning? A case in point is the above-mentioned C chromosome that can sometimes be identified by its secondary constriction. This chromosome can be recognised in several published karyotypes (blood-culture material) and in these it is variously marked as an X or as one of the autosomes 7 through 10. We call it " C′ ", a symbol that has not been compromised as yet.

The analysis of human chromosomes has technical limitations that can be stretched by a search for the exceptional plate but will not yield to a tour-de-force. In many cases the clinical findings complement the chromosomal results to such an extent that those limitations hardly matter—as long as they are respected. But let the cytologist read more into his observations than they contain and the addition of the clinical evidence will merely compound the confusion.

CONCLUSION AND SUMMARY

The Denver report presents biologically meaningful definitions for only 10 of 23 pairs of chromosomes.

It is suggested that authors assign numbers to individual chromosomes only to the extent that there is a meaningful definition or that they provide one, and that their observations suffice to render the identification not merely plausible but reasonably certain.

The work has been supported by Grant C-3313 from the U.S. Public Health Service and Grant T-167 from the American Cancer Society, Inc.

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Occasional Survey

MODERN DEVELOPMENTS IN LIVER SURGERY

THOUGH large and accessible, the liver has in the past largely escaped the surgeon's attention. Today this situation is changing, and planned excision of parts of the liver substance will probably be carried out much more often in the future.

HISTORICAL BACKGROUND

The first successful hepatic resection in man is credited to Berta (1716),[1] who amputated an exteriorised portion of the right lobe. Initial exteriorisation was essential in all operations on the liver until the latter part of the 19th century, when the control of sepsis made possible direct approach through the open abdomen. By 1899 Keen [2] was able to tabulate records of 76 resections with a known mortality of 15% in 74 of them. Nevertheless, up to the time of Warvi's review of 570 collected cases in 1945,[3] an old-fashioned local amputation without regard to the detailed anatomy of the intrahepatic structures was still the usual method. Such operations must often have deprived large portions of the liver of their vascular and biliary connections and it is surprising that infarction, venous congestion, and biliary obstruction, with their baneful consequences of suppuration, hæmorrhage, biliary fistula, and cholangitis, were not commoner.

In the past two decades, the position has been transformed by the adoption of the principle (so fruitfully applied already to the lung and the kidney) of resection in conformity with the units of vascular and ductal distribution, preceded where possible by hilar ligation. The first left hepatic lobectomy by this method is claimed by Pettinari in 1940,[4] and Lortat-Jacob (1952)[5] is credited with the first excision of the right half. Others have followed, and substantial personal series have been recorded by Pettinari [6] and Brunschwig.[7] In the United States, a number of contributions have come from Pack and his colleagues.[8–10] Personal experiences have also been published by several British surgeons [11–14]; and on the continent of Europe at least five monographs have appeared.[6 15–18]

ANATOMICAL BACKGROUND

As with the lung and the kidney, progress has been furthered by new anatomical knowledge, much of it obtained from plastic injection-corrosion specimens. The monographs of Gans [18] and Couinaud [17] give a clear picture of intrahepatic topography and show that the internal arrangement of the liver bears little relation to the lobes of classical anatomy which are bounded only by superficial indentations of no structural significance. The glissonian structures (portal vein, hepatic artery, and bile-duct) divide in the portal fissure into left and right branches whose territories are quite separate, being demarcated by a line running through the gall-bladder bed to the left margin of the inferior vena cava and passing across the division of the portal vein. Each of these halves, or true lobes, is subdivided into four main segments. The venous drainage, on the other hand, is arranged on a totally different plan, the hepatic vein radicles generally running along the boundaries of adjacent glissonian units, receiving tributaries on both sides. Resection of either half is thus, in principle, a straightforward anatomical exercise. The excision of individual segments, however, is less satisfactory, since the hilum of a segment lies within liver tissue and its superficial boundaries cannot be established with precision; it has proved satisfactory only for the lateral and anterior segments of the left half.

REGENERATION OF THE LIVER

Granted normal function in the remainder, excision of a large amount of the liver is well tolerated both by man and by laboratory animals, removal of an estimated 75% being fully compatible with survival. The immediate biological effects of such an operation are incompletely known, but elevation of the serum bilirubin, alkaline phosphatase, and transaminases for several days has been reported, and there may be transient hypoglycæmia with hypoalbuminæmia. Other complex changes in the serum-protein fractions also appear rapidly and last for weeks or even months.[6 8 13 25]

At the same time, the residual liver undergoes startling changes. These have been most fully studied in the rat,[19–21] though similar changes take place in other species, with variations of time scale, and there is much to suggest that the human liver behaves similarly. Between 6 and 12 hours after removal of about 70% of the rat liver, a phase of increased metabolism begins, culminating at about 24 hours in a great outburst of mitotic activity which continues for a further 48 hours, by which time the weight of the residual lobes will have doubled itself. This increase continues more slowly until the original weight is regained at about the 14th day. All elements take part in the process of regeneration, though the parenchymal cells take the lead. What stimulus brings about such an astonishing growth—far in excess of anything seen in the most malignant tumour—is still unknown, but cross-perfusion experiments and investigations on parabiotic rats and on liver-cells in tissue-culture leave no doubt that it is humorally mediated. When regeneration is complete, no defect in liver function can be detected either in the rat or in man.

CLINICAL CONSIDERATIONS

In Italy, an attempt has been made to take advantage of this regenerative impulse in the treatment of hepatic cirrhosis.[6 22] As yet experience is too limited and the results are too recent to allow any conclusions about the value of the method.

With this exception, the conditions for which liver resection can be considered are local lesions, in an otherwise normal organ, so that, granted adequate surgical technique, the ultimate results of treatment are determined solely by the curability of the disease.

Pettinari [6] reports only 1 death (16 months after operation, from unknown cause) among 17 patients who underwent resection for benign conditions, which included anomalous lobes, abscess, hypertrophic tuberculosis, cysts (solitary, multiple, or parasitic), adenoma, and angioma; whereas among 12 with malignant disease (either primary or secondary) only 3 were alive at follow-up (17, 18, and 18 months after operation). Brunschwig,[7] among 22 patients with malignant lesions, had 7 who survived for periods between 4 months and 5 years. Among

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21 reports of patients with primary carcinoma of the liver collected by Reifferscheid,[16] there were 3 postoperative deaths; and of the remainder, 13 survived for periods between 1 and 7 years.

Though with increasing experience postoperative deaths should be almost eliminated, in malignant disease the late results can never show cure in more than a limited proportion of cases. In primary carcinoma the growth is often multiple from the start, especially if it arises in a cirrhotic liver, and all patients may have intrahepatic metastases at a comparatively early stage (though fortunately the secondary growths often lie in the same portal tract as the primary, since they result from invasion of portal-vein trunks; and thus they are resectable). Again, one can never be sure that a seemingly solitary metastatic deposit really is so, though if it first appears some time after removal of the primary growth it is more likely to be.

Further improvement can still be expected from earlier recognition of the disease and greater readiness to perform surgical excision. There are now several diagnostic techniques capable of yielding useful information.[23] Of methods already widely available, two deserve special note —serum electrophoresis and pneumoradiography. Malignant deposits in the liver, whatever their nature, commonly lead to a drop in serum-albumin values coupled with an increase in the α_2-globulin and, possibly, the β-globulin fractions.[24 25] Similar changes are found in other conditions, but none of these is likely to be confused with liver cancer, and, in the presence of such changes, suspicion becomes near certainty.

Presacral pneumography—the radiological outlining of non-opaque organs by insufflating gas into the areolar tissue of the trunk—is already widely known in urological diagnosis. With suitable positioning of the patient, gas can be made to outline the most inaccessible surfaces of the liver—namely, those in contact with the diaphragm and parietes.[6 26] Besides demonstrating irregularities of contour, this method gives a good indication of local spread because infiltrated areolar tissues are impervious and the gas will not pass into them.

In the past, malignant disease in the liver has been generally regarded as inevitably fatal. The results already obtained call for reappraisal of this view. Many cases, indeed, will always be incurable by the time that the diagnosis is made, but prompt investigation and early surgery will save the lives of many who otherwise would rapidly perish. The time now seems to have arrived when at least one surgeon in every major centre should begin to develop a special interest in this work.

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Occasional Book

CHASTITY TODAY

Dr. Eustace Chesser's new book [1] is addressed to anyone who is aware that sexual attitudes change from generation to generation and who wishes to acquire a better understanding of the process. Sexual attitudes in our time are changing rapidly. The modern world (e.g., the Sunday papers) condemns unchastity with every possible cliché, while carefully titillating the appetite for it.[2] As anyone who writes on the subject knows, it is difficult to discuss it freely or in a way that has a practical basis: words must be very carefully chosen; there is a wide gap between what is preached and what is practised; what is beneficial to one person is harmful to the next; what appeals to one, offends another. Thus, much of what is written for the general public has little practical meaning, and it is more or less impossible to approach the subject except in a way that is either unrealistically romantic or else couched in vague terms such as "complete fulfilment", "deep joy", "personal integrity", and "mutual happiness". It is perhaps significant that the British Medical Association's pamphlet,[3] *Getting Married 1960*, has many phrases of this kind. It also contains articles on Should Husbands be Houseproud? and Focus on New Storage Units; but it says little about the practical aspects of sex and nothing about family planning, although the former is usually of great interest and importance to newly married couples, and the latter, in one form or another, affects nearly every couple of childbearing age.

Dr. Chesser is well known for his repeated attempts to discuss sex in the way that present trends demand. In 1959, to the first edition of *Getting Married*, he contributed an article entitled Is Chastity Outmoded? Outdated? Out? [4] which raised such a storm that it was decided to suspend further sales of the booklet. During the controversy, Dr. Chesser was widely attacked and misquoted. He was invited to answer his critics in the Associated Television programme Right to Reply, but when he reached the studio he was told that the programme had been cancelled for reasons of "timing". In view of the considerable publicity which these circumstances attracted, Dr. Chesser wished to present his real and undistorted views, and that is one of his reasons for writing this book. The other is that, from his considerable clinical experience, he believes he can make a contribution to an urgent and perplexing problem.

Dr. Chesser can marshal many facts to support his view that the problem is urgent. There is ample evidence that premarital sexual intercourse is widespread: 1 mother in 4 conceives her firstborn child before she is married; 1 child in 20 is born illegitimate.[5] Questionaries completed by 6000 married and single women showed that 1 in 3 admitted to premarital intercourse.[6] On the basis of these facts, as well as from his clinical observations, Dr. Chesser believes that in recent years we have become confused; many people have thrown over old standards without acquiring new ones. He points out that young people do not necessarily reject guidance, but they ask for guides who speak their language.

Dr. Chesser discusses the meaning of the word "chastity", its interpretation in terms of traditional Christian morals, and the significance of this in the widening gap between the Church and other people which exists today. He emphasises that, despite the modern "relaxed" attitude to sex, there has been no weakening of the family;

1. Chesser, E. Is Chastity Outmoded? London: Heinemann. 1960. Pp. 122. 10*s*. 6*d*.
2. *New Statesman*, March 7, 1959.
3. Getting Married 1960. *Family Doctor* Special. British Medical Association, 1960.
4. Chesser, E. *in* Getting Married. *Family Doctor* Special. British Medical Association, 1959.
5. Wimperis, V. The Unmarried Mother and her Child. London, 1960. See *Lancet*, Feb. 18, 1961, p. 380.
6. The Sexual, Marital and Family Relationships of the Englishwoman (edited by E. Chesser). London, 1956.

in many ways it is stronger than ever before. He summarises the weighty arguments both for and against premarital intercourse. He does not believe that social approval of it would lead to a startling increase of free sexual relationships. Indeed, there might even be fewer, especially of the kind that are most harmful. The situation today drives many young people into sexual unions which they do not desire and from which they do not benefit. For lack of guidance in language they can understand, many believe that " chastity " is outmoded because safety from pregnancy and venereal disease can now be assured. These are false and dangerous beliefs, and so is the argument that legalised abortion is a good way of dealing with a failure of birth control. This kind of information is transmitted verbally and via the walls of public lavatories; it is not counteracted by booklets on the physiology of reproduction or articles on " mutual fulfilment ". Until sex education becomes more realistic, such views will continue to be prevalent, and sexual troubles will continue to be a big problem to society.

Above all, this book is a plea for honest discussion in an atmosphere as free as possible from social taboos and religious intolerance.

Public Health

DIPHTHERIA IN LIVERPOOL

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SINCE 1941 in Liverpool there has been a steady annual decrease in the number of cases of diphtheria:

1941–45	8371 cases	(403 fatal)
1946–50	1345 cases	(55 fatal)
1951–55	49 cases	(4 fatal)
1956–60	7 cases	(1 fatal)

The three years 1956–58 inclusive were the first in which no cases of diphtheria occurred. In 1959, 1 carrier was discovered living within the city boundaries and was associated with an outbreak in the Lancashire area. The local improvement is a tribute to the effectiveness of prophylactic measures introduced during the late war, and continued since. As a result, the level of diphtheria immunisation in Liverpool steadily increased up to 1956 when 45·6% of the child population had active protection. This level of protection has since declined, and the dangerously low level of 36% was recorded in 1959:

1952	41·7%	1956	45·6%
1953	42·5%	1957	43·6%
1954	43·6%	1958	39·5%
1955	44·2%	1959	36·0%

With such a decreasing level of immunisation, it was only a matter of time before diphtheria reappeared in Liverpool. In 1960 two separate outbreaks of diphtheria occurred (3 cases and 3 carriers): in both cases the carrier infection seems to have been contracted abroad.

OUTBREAK 1

A family of 4, comprising 1 adult and 3 children, aged 15, 9, and 7 years, arrived in England on July 7, 1960. They had travelled from Belgium by the night ferry, stayed one night in London, and arrived in Liverpool next day.

Case 1.—On July 10, three days after their arrival in England, the 9-year-old girl had pyrexia and sore throat. A doctor found that she was gravely ill with membranous pharyngitis. Antibiotic treatment was started, and the diagnosis of diphtheria confirmed by finding virulent *Corynebacterium diphtheriæ* type *mitis* on the throat swab. On July 11 she was admitted to the isolation hospital, where she made an uneventful recovery.

Inquiry showed that in addition to her mother, brother, and sister, she had been in contact with 11 known persons in Liverpool, of whom 6 were under the age of 15 years and had no history of immunisation against diphtheria. All known contacts were examined and throat swabs were taken. All were negative for *C. diphtheriæ* with the exception of the girl's brother, aged 7, who was found to be a carrier of the same type of *C. diphtheriæ*. He gave a vague history of a sort throat some two to three weeks before, when in Belgium. This may have been a diphtheria infection and he may have infected his sister before their arrival in England.

OUTBREAK 2

Case 2.—On Sept. 18, 1960, in a different part of the city, a girl of 8 complained of a sore throat on returning home from school. Within forty-eight hours she had membranous pharyngitis and a " bull neck ". A clinical diagnosis of diphtheria was made. On admission virulent *C. diphtheriæ* type *mitis* was isolated from both throat and nasal swabs. Despite treatment she died ten days later from toxic myocarditis.

No connection between case 1 and this 2nd case could be established in spite of the relative short time-lapse (ten weeks) and the bacteriological finding that both organisms were of the same type. The two incidents were thought to be completely separate.

31 classmates were examined on Sept. 20. With one exception, all throat swabs were negative for *C. diphtheriæ*. The exception was that from an 8-year-old girl which yielded virulent *C. diphtheriæ* type *mitis*. She was a close school companion of case 2. She had not had symptoms and was considered a carrier. Admission to hospital was arranged on Sept. 25, 1960.

This carrier, with her mother, father, brother aged 6, and sister aged 9, had returned to England a fortnight previously (Sept. 11) after a five-week holiday in Cyprus. These home contacts were examined and throat swabs taken. The 9-year-old sister was also found to have virulent *C. diphtheriæ* type *mitis* in her throat. She also had not had symptoms and was considered a carrier.

Despite close questioning, a recent history of tonsillitis could not be obtained in these 2 girls, though the 8-year-old sister had had pyrexia for two days when on holiday in Cyprus (? mild diphtheria). Both were successfully treated in hospital.

Case 3.—Virulent *C. diphtheriæ* type *mitis* was isolated on Sept. 27 from the throat-swab of the 6-year-old sister of case 2. Clinically she had a mild pharyngitis and she complained of feeling unwell. She was successfully treated in hospital. Her throat swab had been negative for diphtheria organisms when examined seven days previously. On both occasions the home contacts consisting of mother, father, brother aged 11, and sister aged 13 years were negative.

In this second outbreak neither case had been previously immunised against diphtheria. Of the 31 classmates, only 11 had been immunised; 15 had no protection; and with the remaining 5 the parents could not remember if they had been immunised against diphtheria. Both carriers had been protected in infancy against diphtheria.

PROTECTIVE MEASURES

In the first outbreak there were fortunately only 11 known contacts. These children were protected by simultaneous administration of antitoxin and antigen, a

procedure suggested by Downie et al. (1948). Alum-precipitated toxoid (A.P.T.) was chosen because at that time Liverpool was free from poliomyelitis and despite the slight risk of provoking the disease (Medical Research Council 1956) it was thought that a potent antigen such as A.P.T. was more likely to lead to a satisfactory level of immunity in the presence of small amounts of antitoxin.

In the second outbreak there were many more contacts, and wide publicity. Within fourteen days of the fatal case, 14,646 children were given primary immunisation and 9559 received booster doses. Children up to 5 years were given D.T.P. (diphtheria-tetanus-pertussis). Children between 5 and 10 were given combined diphtheria-pertussis prophylactic or formol toxoid (the choice of antigen depended upon whether there had been a previous history of whooping-cough). Toxoid-antitoxin floccules (T.A.F.) were given to young persons over 10 years.

Schick-testing was carried out in cases where there was a doubtful history of previous immunisation or in those with a known history of allergy. During this period 210 schoolchildren were tested, of whom 83 gave a negative Schick reaction; these were protected as described.

DISCUSSION

In both outbreaks an unsuspected carrier was thought to be the original source of the clinical disease. Case 1 could have contracted her infection from the 7-year-old brother. Case 2 was infected by a classmate, and case 3 acquired the disease from her sister (case 2).

It was of interest to find 2 carriers in the same family (8 and 9 years old) both of whom gave a history of primary immunisation (7 and 8 years previously). The 8-year-old carrier was discovered on the first throat-swabbing of the class of schoolchildren. Her 9-year-old sister was negative on this occasion, but positive for *C. diphtheriæ* one week later (second throat-swabbing). Both children had not received any form of booster protection following their primary immunisation. This raises the question whether the 9-year-old girl was indeed a carrier or whether she was an undiagnosed 4th clinical case.

In a recent outbreak of diphtheria in Barking, Groarke et al. (1960) discovered 12 cases and 14 carriers among 127 schoolchildren at risk in an infant school. 11 of the carriers were from the same affected class, and the investigators of this outbreak could not decide whether a positive bacterial finding indicated a case or a carrier, even though in their outbreak there was no known history of previous immunisation in the doubtful carriers.

A common feature in the Liverpool cases was the history of recent travel abroad, and the infection may have been contracted outside this country. On the other hand, the virulent *mitis* type of *C. diphtheriæ* has been found within recent years in England, being last isolated in Liverpool in 1954. The single fatal case in 1955 and the carrier traced in 1959 were both due to a virulent *intermedius* type of *C. diphtheriæ*, and both incidents were associated with cases in the Huyton area of Lancashire.

The restricted movements of case 1 enabled the health department to give adequate and swift protection to the known contacts without press publicity or public reaction. Case 2, ten weeks later, unfortunately had a fatal ending. This received wide press publicity, local and national, especially because there were similar outbreaks of diphtheria occurring in the country at that time. In consequence, a heavy demand for immunisation was made both on the health department and on general practitioners. In the fourteen days after the fatal case a total of 24,205 children were given primary or booster protection against diphtheria (14,220 by the health department and 9985 by general practitioners)—an indication of the relatively low immunity within the school population and also of the degree of anxiety among the parents.

SUMMARY

In 1960 two outbreaks of diphtheria involving 3 cases (1 fatal) and 3 carriers occurred in Liverpool. In both outbreaks the infection may have been contracted abroad.

In the first, 11 known contacts were protected with alum-precipitated toxoid.

In the second, in which 1 child died, there were more contacts, and within fourteen days 14,646 children were given primary immunisation and 9559 received booster doses. Children under 5 were given D.T.P. (diphtheria-tetanus-pertussis); children between 5 and 10 were given either combined diphtheria-pertussis prophylactic or formol toxoid; and those over 10 received toxoid-antitoxin floccules.

At the beginning of the second outbreak, the level of protection must have been dangerously low, because in 1959 only 36% of the child population of Liverpool had active protection.

We wish to thank Prof. D. T. Robinson and Dr. E. C. Armstrong, of the Public Health Laboratory Service, Liverpool, for the examination of nasal and throat swabs.

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Medical Research Council (1956) *Lancet*, ii, 1223.

Ocular Ochronosis

THE list of prescribed industrial diseases has been extended to include ocular ochronosis due to exposure to quinone or hydroquinone.[1] A person contracting the disease at work will be covered for the benefits of the Industrial Injuries Scheme from April 28. Although the disease is rare, and stringent precautions are taken, occasional cases have arisen during the past few years.

Parliament

The "Special" Hospitals

ANNOUNCING the publication of the report on the "special" hospitals,[2] Mr. ENOCH POWELL, the Minister of Health, said that its main recommendations were as follows:

1. All three hospitals should be used for patients with dangerous, violent or criminal propensities, whether they had been before the courts or not.

2. Patients in these hospitals should be grouped according to their medical needs and there should be greater specialisation.

He accepted these recommendations and was considering the rearrangements which would be necessary at the hospitals.

3. Patients should be accepted for admission to the hospitals only after other possibilities had been carefully examined and found to be unsuitable.

4. To reduce the need for admissions to these hospitals, regional hospital boards should arrange their psychiatric services so as to provide various types of hospital unit including some secure units.

He accepted these recommendations. Hospital authorities had been asked to implement no. 4, and would be advised on the steps they should take to enable him to implement no. 3.

1. National Insurance (Industrial Injuries) (Prescribed Diseases) Amendment Regulations 1961, s.i. 1961, no. 691. H.M. Stationery Office. 3*d*.
2. See *Lancet*, April 22, 1961, p. 868.

5. Diagnostic and treatment centres should be provided within the National Health Service for patients who presented exceptional difficulty because of their aggressive, antisocial, or criminal tendencies combined with special problems of diagnosis, treatment, and management. One or two such centres should be provided initially to gain experience.

He was discussing the establishment of such centres with certain regional hospital boards.

Home Safety Bill

ON April 21, Mr. A. P. COSTAIN'S Home Safety Bill received its third reading. The Bill, which has the support of the Home Office, enables minor county borough councils and urban and rural district councils to take part in home safety propaganda and to give funds to voluntary bodies. At present only major authorities have these powers.

Meals-on-Wheels

IN the House of Lords, on April 18, Baroness SWANBOROUGH drew attention to the need to expand meals-on-wheels schemes. She urged that local authorities should be authorised to provide kitchens and other equipments and facilities for voluntary bodies who were running these schemes. Under the National Assistance Act 1948 and the National Health Service Act 1946 local authorities had some powers to make grants to voluntary bodies providing meals for old people or for invalids respectively, but the nature and amount of help they gave varied. Some subsidised meals, some provided equipment, some bought and maintained vans. Sometimes two or more authorities contributed to the same scheme, which could work well or could lead to parsimony. So far as voluntary organisations could discover, there was no clear ruling whether, under the National Assistance Act, authorities had the power to incur capital expenditure to provide kitchen and vans. Central authoritative advice would be most useful in helping to clear doubts as to how existing legislation could be interpreted.

Lord AMULREE pointed out that many people who used the meals-on-wheels service were on special diets and he thought that they should be supervised by someone with knowledge of nutritional values. He also believed that the service should be available on five days a week in all areas and that where there was difficulty in finding volunteers authorities should be able to employ people to run the service. He wondered whether it would not be more satisfactory if a comprehensive service of this kind was to become part of the National Health Service

Lord ST. OSWALD said that in 1959 the Government had promised to introduce legislation to enable local authorities to make direct provision of meals Since then there had been the helpful report of the Government Social Survey [1]: in the light of it the Minister was now considering how best to frame legislation for " meals-on-wheels ". Authorities who were doubtful about their present powers were free to ask the Ministry's views.

QUESTION TIME

Mental Health Review Tribunals

Mr. KENNETH ROBINSON asked the Minister of Health if he was satisfied, in view of the small number of applications to mental health review tribunals, that patients detained in hospital were generally aware of the existence of the tribunals. —Mr. ENOCH POWELL, the Minister of Health, replied: Hospitals and mental nursing-homes have been asked to give detained patients and their nearest relatives a statement of their rights, and a series of leaflets is supplied for this purpose. I have no reason to doubt that the request is being complied with. Mr. ROBINSON: Nevertheless, would not the Minister agree that 86 applications up to the middle of last month is fewer than anybody envisaged at the time of the passage of the Mental Health Act? Mr. POWELL: I do not think the small number until recently is significant, because, up to the end of April, only a very limited number of patients had the right to apply. We shall get a much better idea of how this is working from now onwards.

1. See *Lancet*, Jan. 28, 1961, p. 235.

In England Now

A Running Commentary by Peripatetic Correspondents

THE London season was duly launched when the Royal Academy of Arts opened its one-hundred and ninety-third annual exhibition at Burlington House last Wednesday. First over the fence, as usual, in the mad pursuit of culture, your peripatetic dutifully tore himself away from the gay social whirl of the labs, wards, and mortuaries of St. Q's to search on your behalf for medical undertones, overtones, and even tones, among the 1393 pictures, sculptures, carvings, drawings, architectural designs, *objets d'art*, and *objets* with no *d'art* about them whatever. The sheer bulk of the show is usually exhilarating; but this year, with the Platt Committee's sob still ringing in one's ear, one could not help counting the senior casualty-officers, assistants in geriatrics, and child psychiatrists who have been lost to our profession by taking up painting or sculpting. Unless, of course, you still believe that medicine is an art as well as a science. Still, bad art is often more fun than good art, and it is said to be more instructive about what historians call the social climate of the age. If this is true, we must expect no cyclones or anticyclones for at least a decade. Reynolds, whose statue broods over the forecourt, reproached Hogarth and his followers in one of his presidential and (until resurrected by Professor Pevsner) justly neglected Discourses, because they painted nothing but " the various shades of passion as they are exhibited by the vulgar mind ". Granted that statistically the number of exhibitors with a tenth of Hogarth's talent is profoundly insignificant, passion—vulgar or refined—is the element most conspicuously lacking in 1961. Last year we were treated at least to some posthumous Stanley Spencers—and what a treat they were! This year love, hate, hope, despair, heroism, and suffering—the human ingredients of medicine—are swamped by rows of Sunsets in Portofino, Wet Afternoons on the Boulevard d'Italiens, Views on Kew, Mountainous Landscapes from Nepal, Doves, Gardens in Croydon, and (practically singlehanded in Gallery IV) by a staggering *Dinner given by the Gentlemen of the White Collar of Pytcheley Hunt, at Althorp, April 1960.* Fuseli (a good Swiss as well as a patriotic Englishman by adoption) said that Constable's pictures made him call for his greatcoat and umbrella. Today Mr. R. A. Thomson would presumably set him off looking for his interstellar rocket. Almost alone Normal Blamey's *Physiotherapy* conjures up some of the horrors of the Spanish Inquisition, and Roy Noakes's impressive *Crouched Figure* illustrates a more contemporary curse of what we are pleased to describe as our sedentary civilisation.

Medical portraits are usually grateful targets for the percipient viewer; but none are exhibited this year. (Your correspondent was thrilled to catch a glimpse from across three galleries of what he fondly imagined was the Editor of *The Lancet* in full episcopalian regalia. Alas, it turned out to be the Bishop of London.) This is not only rather shameful but also difficult to understand. There may, of course, be more practical means of commemorating the retirement, after years of devoted service, of a medical-school dean, college president, or senior surgeon; but not even memorial lectures could make the event more deeply regretted than a State portrait by Mr. James Gunn or Mr. Edward Halliday. However, perhaps doctors nowadays—unlike lawyers, headmasters, debs, duchesses, and prime ministers—regard their faces as conveniences rather than as ornaments.

If you happen to pass Burlington House, a splendid exhibition of Landseer drawings is still open in the Diploma Gallery.

* * *

Her hair was dripping wet as she slumped from the hairdresser's chair and presented the assistant and the management with a problem they hadn't met before. She had had to rush to keep the appointment after an unexpected brush with a tiresome typist in the office, but she was only a few moments late for the styling-shampoo-and-set. Her sister, who had an

appointment some 30 minutes later, was approaching the hairdresser's when an ambulance passed and stopped at the door of the shop. "No! It can't be! Yes, it might be Joan!", and she ran the remaining distance in nearly Pirie-time. Joan lay on a stretcher, out to the wide, and was being lifted, when Molly intervened. "It's no use taking my sister to hospital, because she's an epileptic; they know her there and will just leave her until she comes round and then send her home. Just let us take her home now!" But the ambulance driver expostulated: "You just can't call an ambulance to take a person home! It's not allowed! We'll have to take her to hospital!" "But, wait," pleaded Molly, "we're near the hospital here, and our house is on your way back to your depot, so no-one will know that you haven't taken my sister to the hospital, because we won't tell anyone!" It worked. The driver beamed in compromise, "All right; then we'll take your sister home if you will say she refused hospital treatment. That is allowed."

* * *

Gurkhas are generally fond of doctoring in all its forms, though a rather childish fear of injections makes immunisation sessions take longer than they should. But mere fear was not enough to prevent a mother claiming what seemed to be her baby's rights; so when junior's first jab of triple antigen failed to "take" like the smallpox vaccination some weeks before, she came back to the clinic, complaining loudly.

* * *

"So you're over the road at the 'ospital are yer? Used to be on the staff meself there years ago. Mornin' sessions—8 to 10 in the private wing. But it was 'opeless. Could never see anyone on me rounds. When I arrived Mr. So-and-so was 'avin' 'is breakfast, Sir So-and-so was in the bath, and Lord So-and-so was busy poshin' 'imself up. Lucky I was if I saw three patients in 2 hours. Terrible waste of time. But that wasn't the worst of it—one night at about 11 the phone goes and the missus tells me I'd better pull on me clothes and go quick—they need me for an emergency. So I rush out 'alf dressed, throw meself on the last Tube and come pantin' into the 'ospital just before midnight. And what do I find? They're gettin' along great and 'ave forgotten all about me. The surgeon decided he couldn't wait so he just shaved the 'ead 'imself. That was the last straw. Next mornin' I resigned me post as part-time consultant 'airdresser. But they still call me in occasionally . . ."

* * *

The influence of the Census is manifest even in applications for consultant appointments:

Age and Nationality—I was born on May 27, 1923, unmarried, and a British subject.

* * *

He was a splendid old man of over 90, and even after prostatectomy for retention he didn't turn a hair. He could hardly see, but he recited at length from his own compositions with hardly a falter. The one we liked best had been written in his 80s and had been inspired by a friend who had patiently borne many years of severe arthritis. They had been sitting on a bench together when a sudden movement caused his friend to grunt with pain and make the remark which is the title of the poem:

I GRUNT BUT NEVER GRUMBLE

"I thank the Lord for all the good,
As out of bed I stumble,
I feel the cold, I'm getting old—
I grunt but never grumble.

My friends are true and kindly too.
My home is warm, if humble,
I have good light, the fire shines bright—
I grunt but never grumble.

I have no fear for God is near,
He will not let me stumble,
I would not dare to doubt his care—
I grunt but never grumble."

Letters to the Editor

HUMAN RELATIONS IN HOSPITAL

SIR,—When the report on Human Relations in Obstetrics was published, the Minister announced that he wished management committees to report to him by the end of July on their responses to the report. I feel that our whole profession must view this as a sign of rising interest in that aspect of medical practice which might be called Consumer Satisfaction. Such interest is not confined to the work of the maternity services.

Perhaps we have reason for professional shame in the fact that the lead in demanding changes does not appear to be coming from doctors. But it seems likely that only a rapid response by us to these demands for change can protect our profession from a sharp fall in public affection and respect. The greatest need for action seems to be in hospitals; certainly, the best openings for organisational action are there, and that is the response I advocate.

When the "Hospital *Staph.*" became notorious, committees were formed to collect information about episodes of cross-infection, to examine the procedures in use throughout hospitals, and to suggest changes in practice. Notoriety may now be said to be migrating to the Hospital Staff, and I suggest that each hospital needs an organisation for the collection of information from dissatisfied patients, the examination of procedures in use, and the suggestion of reforms. I believe it is essential that action on this matter should be as urgent as it was on the matter of cross-infection, and I hope that no-one will feel that tender care for the feelings of patients is less proper to medicine than the extermination of pathogenic bacteria.

An author in the lay press gives an example of the need for organisational action: "It is the rare hospital which has a consultant in charge of its casualty department. In most, there is no one in charge. This means there is no one to report to a higher administrative authority on ways to improve the service." [1]

Some may say that it is the duty of the management committees to see to this question. Since the existence of a great number of management committees has not protected us from the present unsatisfactory state of affairs, it is useless to leave the work to them. Furthermore, such a step would not, in my opinion, involve the curative professions of medicine and nursing closely enough in the task of setting their own house in order. I hope to see the lead regained from the laity.

I do not feel attracted by the idea of a subcommittee of fixed, limited membership. I favour the idea of a club of enthusiasts whose meetings would be open to any well-wisher among the staff. When I was a medical student and viewed a hospital with a fresh eye, I had a much more lively impression of the lack of deep concern for the comfort and the comforting of patients than when I had become part of the machine. If this development is general, then it will be the most junior staff who will be most ready to ask "why must it be done that way?" If everyone in the hospital who could contribute one suggestion were a permanent member of the club, it would be too big; if they were always excluded, ideas would be lost.

Members of the club would gather ideas by using their own eyes and ears in wards and waiting-rooms, and by reading the contents of "suggestion boxes" provided for contributions from patients. They would also report at meetings on the many valuable comments to be found in journals and in fiction. A bibliography of these comments would be valuable, and a national association of enthusiasts for this work would form

1. Catling, S. *Spectator*, April 14, 1961, p. 504.

one. Many national associations already represent those "consumers" of our services who feel neglected.

The executive actions of the clubs would be of two sorts: recommendations to the management committee or regional board for administrative action; and personal campaigning to mould the "public opinion" in the hospital in regard to matters such as brusqueness or inhumanity. The clubs might have to take a firm stand against pressures tending to make them degenerate into bodies for the investigation of serious complaints. If they became associated in people's minds with the issuing of reprimands, they would be too unpopular to continue with the initiating of reforms.

In a survey [2] of the maternity services, you discussed "errors of attitude?" and wrote: "There is widespread agreement about what in general should be done; but practical suggestions as to *how* it should be done are fewer and often conflict." Here, then, is a practical suggestion, on which critical comment is invited.

Southport Infirmary,
Southport, Lancs. D. MACSORLEY.

α-PHENOXYPROPYLPENICILLIN

SIR,—In your leading article of April 22 entitled Antibiotic Policy and the Staphylococcus there appears the statement "Like methicillin, PA-248 (α-phenoxypropylpenicillin) remains active in the presence of staphylococcal penicillinase; . . .".

This gives the impression that α-phenoxypropylpenicillin is a new penicillin similar to methicillin ('Celbenin') in its stability to staphylococcal penicillinase. This is completely untrue. α-Phenoxypropylpenicillin is in fact destroyed very rapidly by staphylococcal penicillinase and to compare it with methicillin, which is completely stable, would be very misleading indeed.

On the other hand, compared with phenethicillin (α-phenoxyethylpenicillin) ('Broxil') it is true that α-phenoxypropylpenicillin is slightly more stable to penicillinase and this is reflected in slightly better minimum inhibitory concentrations (M.I.C.) values against resistant staphylococci. However, it should be emphasised that these M.I.C. values for α-phenoxypropylpenicillin against resistant staphylococci depend entirely on the size of inoculum used in the test (as is the case with penicillin G itself) and these in-vitro figures which might suggest that this antibiotic may be of value in the treatment of resistant staphylococcal infections are obtained only if the penicillinase factor is small. This point is illustrated in the table below in which M.I.C. values are given for α-phenoxypropylpenicillin with different inoculum sizes.

	Minimum inhibitory concentrations of α-phenoxypropylpenicillin in broth culture (μg. per ml.)	
Inoculum (overnight broth culture)	*Staph. pyogenes* strain BRL. 1083 (penicillin-resistant)	*Staph. pyogenes* strain Russell (penicillin-resistant)
1 drop (0·03 ml.)	> 500	250
1 drop of a 1/100 dilution	0·5	0·25
1 drop of a 1/100,000 dilution	0·12	0·05

It should be clearly understood that α-phenoxypropylpenicillin is a penicillin with properties very similar indeed to those of phenethicillin, and it should in no way be confused with methicillin which is unique in its activity against penicillin-resistant staphylococci.

Beecham Research Laboratories Ltd.,
Brentford, Middlesex. G. N. ROLINSON.

SHORTAGE OF HOSPITAL STAFF

SIR,—I should like to endorse wholeheartedly Dr. Hampson's letter (April 15) on the shortage of medical laboratory technicians, and emphasise the most important and potentially dangerous aspect—the difficulty of organising emergency blood-transfusion services at peripheral hospitals.

Provisionally registered housemen (assuming you are lucky enough to have any) are neither trained, nor willing, to perform emergency cross-matching. Indeed, if busily occupied dealing with patients, it is quite impossible for them to find time for satisfactory cross-matching. Even if they were willing, they have been advised not to do this work for medicolegal reasons.

Thus the bulk of these emergency duties inevitably falls on laboratory technicians; and the limited numbers of trained technicians willing and available in the smaller hospitals may mean that they have to be on call at home on two or three nights a week and every second or third weekend, for which they get paid nothing unless actually called out.

The so-called "contingency service" as described in circular HM55(14) is quite meaningless except perhaps for the very small cottage hospital. How can you admit casualties and maternity emergencies when conditions are such that ". . . the hospital will do its best to carry out the test providing it can reach the pathologist or technician . . ." Meanwhile the patient presumably bleeds to death!

Therefore a guaranteed service must operate, and this means serious domestic disturbance for technicians who have to be on call and must be prepared to come to the hospital at any hour of the day or night and perform serological tests which, should an error be made, may result in the death of the patient and lengthy legal proceedings afterwards.

I find it difficult to believe that laboratory technicians outside the hospital service have a "pattern of responsibility" anything like as onerous as this. It is hardly surprising that under present conditions there is a shortage of people to take on these highly responsible duties. The basic salary and payment for emergencies need to be substantially increased if recruitment is to be maintained. If it is not, a situation may arise when we would have to advise hospitals, in the interests of the patients, to refuse admission to emergencies requiring blood-transfusions, and patients would have to be sent many miles to the nearest teaching hospital or large provincial hospital with adequate laboratory and medical staff.

Pembury Hospital,
Tunbridge Wells,
Kent. W. M. R. HENDERSON.

SHORTAGE OF RADIOGRAPHERS

SIR,—Many of your correspondents have suggested admirable means for increasing recruitment of radiographers. Perhaps the time is opportune to put forward a different approach.

Each year we have to reject several applicants who have all the qualities of good radiographers, but for various reasons, for which they are often not responsible, they have not passed mathematics at ordinary level in the G.C.E. The Society of Radiographers insists on a pass in mathematics as well as in English before accepting candidates for the examinations for membership of the Society (M.S.R.). This makes a curious contrast with The Chartered Society of Physiotherapy by whose regulations mathematics is an optional subject, although I understand that in ordinary physics (as opposed to radiation physics) their syllabus reaches a level at least as high as that required by the Society of Radiographers. It may well be argued that the possession of mathematics at ordinary level makes the teaching of physics easier for the instructors; but for many years before the new regulations were introduced students without a pass in mathematics have passed the M.S.R. examinations with relative ease.

In recent years great advances have been made in X-ray apparatus and many innovations have been introduced to

2. *Lancet*, April 22, 1961, p. 874.

remove the human error. Automation obviously provides the answer to standardisation, and also to the shortage of radiographers. In Sweden the trend to do away with technical assistance is evident and gradually the transition will occur in this country as the financial situation permits. As apparatus becomes more complicated it gets quite beyond the understanding of the average radiographer—to say nothing of the radiologist—and the need for a resident engineer becomes more important than a mathematically-minded technician.

In the meantime, however, all the resources that can be mustered should go to providing technicians who can produce good radiographs and treat patients with kindness and understanding. These are practical skills; and gaining the M.S.R. without a practical examination gives no guarantee of these qualities.

Without wishing to detract from the admirable ambition of the Society to raise the level of education of their members, I feel that by insisting on mathematics as a compulsory subject they are failing to make a practical contribution to the solution of a national problem.

Department of Diagnostic Radiology,
The United Leeds Hospitals. A. S. JOHNSTONE.

RESTITUTION OF INTERNAL CAROTID ARTERY

SIR,—I think most surgeons would agree with the facts and statistics largely derived from reviews by Edwards et al.[1] and Riishede et al.,[2] which you quoted in your annotation (April 15). Fewer would agree on the general tenor of the conclusions that (on the whole) the operative treatment of arteriosclerotic lesions of the cervical arteries is likely to be dangerous and unsuccessful.

It is clear that operations on completely occluded carotid arteries appear to be of little immediate benefit in that the neurological signs seldom improve. What is not determined is whether the increased cerebral blood-flow which sometimes results is of any prophylactic value against further attacks of vascular insufficiency. The effect of restoring complete patency to a partially obstructed vessel is also, as you suggest, uncertain, because there are not yet enough reports of patients whose attacks of transient hemiparesis have become less frequent. The reports so far, and our growing experience, do make it clear that the mortality and morbidity of endarterectomy and by-pass operations is exceedingly small; and this justifies a less conservative attitude than you adopt in your annotation. Few surgeons would agree that there is a danger of showering emboli into the brain from a lesion which is cut off from the general circulation during exposure.

I would suggest that the operations at our disposal will very seldom do harm, and may very well be beneficial in preventing or postponing hemiplegia. In any event it is too early to condemn them after analysing only the first 70 cases from London and Copenhagen. By being unnecessarily discouraging about the results of an operation so far insufficiently tried you are tending to close a half-opened therapeutic door which you might equally well, by a slight shift of emphasis, push open. In the treatment of carotid arteriosclerotic lesions inactivity has given poor results. The anticoagulants and sympathetic denervations are of very doubtful value; surgery, carrying a very low morbidity, may improve the prognosis. This can only be shown by large series of operations; and we should push towards the goal of obtaining this information rather than falling back on a conservative regime known to give poor results.

The statement that carotid compression leading to convulsions or unconsciousness is dangerous is hard to gainsay. It should not be taken to mean that temporary occlusion of a carotid artery is dangerous. It is certainly the single most valuable clinical method of assessing insufficiency—much more helpful than pharyngeal palpation of the carotid artery, auscultation, or the estimation of retinal-artery pressure. If it is explained to the patient that he must indicate fullness in the head, clouding of consciousness, or paræsthesiæ of a limb, and if in addition he is asked to count aloud slowly while his artery is occluded, the compressing thumb can be removed on the first appearance of abnormality and the manœuvre is without danger. It is not necessary to produce a level of local anoxia which would cause convulsions or unconsciousness.

In sum I would suggest a more enterprising attitude to both diagnosis and treatment in this vastly interesting field of cerebral vascular insufficiency. I think we are justified in pursuing a policy of large-scale in-vivo experimentation in the knowledge that such a policy carries negligible risk to the patients and may considerably benefit them.

Department of Neurological Surgery,
Royal Victoria Hospital,
Belfast. ALEX R. TAYLOR.

1. Edwards, C. H., Gordon, N. S., Rob, C. *Quart. J. Med.* 1960, **29**, 67.
2. Riishede J., Ottosen, P., Søndergaard, T. *Danish med. Bull.* 1960, **7**, 185.

SIR,—It was with great interest that I read your annotation; but I am surprised that you thought fit to mention the importance of ophthalmodynamometry in the diagnosis of carotid insufficiency in such a fleeting and inaccurate way.

The technique of dynamometry is not new. Numerous papers describing excellent results from the procedure in diagnosing carotid insufficiency have appeared in the American press over the last 10 years, and are now finding their way into British journals. By using this procedure in Manchester alone 400 patients a year are screened for carotid disease; and the results from this clinic suggest that dynamometry diagnoses over 90% of cases of carotid insufficiency of all grades of severity.

It is a pity you did not reveal this aspect of the procedure but only quoted derogatory opinions of workers from overseas. Indeed, the expression "measurements of the . . . retinal arterial pressure" reveals your basic misunderstanding of the theory of dynamometry, which under no circumstances measures the pressure in either the central retinal or ophthalmic arteries, but provides an arbitrary measure of the pressure in the ophthalmic artery, which is of value only as a comparison with the similar reading from the other eye of the same patient.

Furthermore, dynamometry offers a safe alternative to angiography, a point in favour of further and wider application of the technique.

Manchester Royal Eye Hospital,
Manchester. V. H. SMITH.

HOUSING

SIR,—I am extremely glad you published Mrs. Harvey's letter (April 15) about the housing shortage. But if doctors flooded the London County Council with medical certificates for rehousing, I am not sure it would benefit those whom they were trying to help. It is often difficult to decide when bad housing becomes a medical matter, since the total problem usually involves so many other factors, especially when mental illness is present. After all, it is common sense, not medical training, that tells one that living 4 or more to a room is an inhuman strain on any family.

If doctors, as members of a profession with exceptional opportunities for insight into human needs and dignity, would organise a protest against the terrible conditions under which so many people live at present, I for one would certainly support it.

London, N.W.3. PHYLLIS DOBBS.

*** Because of the very large number of medical certificates for rehousing (e.g., 44,000 in 1950, the L.C.C. has since 1957 asked doctors to send a letter instead; between 40 and 50 a week are received.[1]—ED. L.

1. See *Lancet*, 1960, ii, 1396.

NOT FOR SALE

SIR,—After a special meeting of the Consultants and Specialists Committee (no. 13 region) on Monday, April 17, at Preston Royal Infirmary, the following statement was issued to the Press.

"The Manchester Regional Consultants' and Specialists' Committee has considered allegations of improper professional conduct made by Dr. A. A. Dunlevy in a recent letter to *The Lancet* and in subsequent television and radio broadcasts. If any such allegation be true, this Committee condemns such conduct as repugnant to the ethics of the medical profession, and is satisfied that this condemnation would be supported by our fellow consultants and specialists throughout the United Kingdom.

"The Committee invited Dr. Dunlevy to attend this evening's meeting, to give him full opportunity for substantiating his accusations, but he declined to come. He has also failed to send us any specific complaints which we could investigate. This Committee is, of course, unable to compel the attendance of any doctor at its meetings, and must therefore content itself with the clear expression of its views on professional conduct given above".

H. MILNES WALKER
Chairman,
Manchester Consultants & Specialists Committee.

SIR,—I read with interest the result of the Preston meeting of the Manchester Regional Consultants and Specialists Committee. The fact that they are now prepared to deal with the matter as a serious one is a wonderful step forward since 1960 when the spokesman for the local B.M.A. refused to discuss it.

Obviously the fact that I did not accept the invitation to attend this meeting is open to misinterpretation. However, my reasons were fully stated in my reply to Mr. Milnes Walker. Briefly they are:

(*a*) The Consultants and Specialists Committee of the B.M.A. is part of a voluntary organisation. It is not a statutory body and has no legal standing. A member of the B.M.A. could give evidence in front of it and this would be an occasion of qualified privilege. I am not a member of the B.M.A.—therefore my evidence would not be an occasion of qualified privilege.

(*b*) I feel this matter is of such importance that my evidence alone is not sufficient. To be really effective, we must be in a position to bring patients forward to give their evidence, and we must also be in such a position that these patients are protected.

Finally let me state that I am anxious to put all the evidence I have before any committee set up by the Minister of Health. This inquiry should have an independent, impartial, and legally qualified chairman and should have power to subpœna witnesses.

Withington Hospital,
West Didsbury,
Manchester.

A. DUNLEVY.

THYROID FUNCTION IN THE PRESENCE OF BREAST CANCER

SIR,—We observed [1] that in patients with carcinoma of the breast those with local disease only (stages I, II, and III) had, on the average, normal thyroid function, while those with blood-borne metastases (stage IV) appeared to have significantly lower function. Mr. Reeve and his colleagues (March 25) have been unable to confirm these findings. However, they do not draw attention to the fact that their data reveal lower function in patients in stages II, III, and IV (combined mean in their units = 0·316) than in those in stage I (0·444); *t*-test for significance gives $P < 0.05$. (We are grateful to Mr. J. D. Merrett for this analysis.)

They attribute to us the suggestion that "metastases in the pituitary or in the thyroid or in both may destroy functioning tissue". We certainly used these words but concluded that this was an *unlikely* cause of depressed thyroid function.

Department of Surgery,
Institute of Clinical Science,
Belfast.

G. A. EDELSTYN
A. R. LYONS
R. B. WELBOURN.

1. Edelstyn, G. A., Lyons, A. R., Welbourn, R. B. *Lancet*, 1958, i, 670.

CARE OF THE INJURED

SIR,—There is so much wisdom in Mr. Devenish's letter of April 8 that one wonders what can be in dispute. Any conclusion, however, that all is well is belied by current experience of the inadequacy of treatment of injuries. Shortage of staff is clearly an important limiting factor—we would suggest that a deliberate policy could make the best use of what is available.

It may well be that London is a special case; the development of its hospital services has been different, and its solution of the problems of accidents may also be different. In the rest of the country, large cities, towns of various sizes, and rural areas, the background is not the same; and though services are good in some areas, there are many gaps. The problem is how best to fill these gaps.

The special needs of the seriously injured patient derive from the following:

(a) Injuries occur at all times, with an important peak late at night. A few take place in the small hours, and these are often the most severe.

(b) The successful management of most of these cases requires urgent first-class diagnosis and surgery.

(c) Many of the injuries are multiple. They have features in common in respect of shock, &c.; but they do not fall naturally into any one of the present specialties. Their treatment often requires special experience and judgment rather than special technical skill.

For these needs to be met there should be a fully equipped accident service within reasonable distance of any accident. The service must be staffed by fully qualified surgeons; and they should be genuinely, and not only nominally, available throughout the twenty-four hours. There is a size below which an accident service becomes inefficient and uneconomical; this is the rationale behind the need for "centres". Other hospitals may be able to give adequate service during the day, but need to redirect patients to the "centres" at night; in this sense some "coordination" would be beneficial. This incidentally implies more, not less, efficient use of ambulance services. The staff requirements for such a service include nurses, X-ray and laboratory staff, and surgeons. At present valuable help comes from surgeons from the Commonwealth and elsewhere who visit us to complete their training. All these are more likely to be attracted if there is a clear policy and enthusiasm for first-rate accident work. This same environment is ideal for research into both the clinical aspects and the causes and prevention of injuries. There should be a career structure as Devenish suggests, and this could be eased by providing teaching and research at the "centre" with exchange of staff between "centre" and periphery—in this sense also "coordination" is valuable.

The present improvements in some areas are largely the result of recent increased interest in this problem, coupled with the enthusiasm of surgeons such as Mr. Devenish. An organisational structure however is required which will maintain and develop such services when the present interest wanes, and will prevent the reversion of accident treatment to its previous state of dependence on junior staff. Disagreement and confusion have arisen in an attempt to allocate accidents to one or other of the established specialties. Since multiple injuries affect so many parts of the body it seems that a general surgeon with special interest in injuries is required. A variety of

specialists may have to be called in later, but the urgent need is for a surgeon, whatever his official specialty, to be responsible for the whole patient and to attend to him without delay. The facilities for accident treatment can probably best be provided in an accident department attached to a general hospital where it can benefit from liaison with other special departments. But there is a strong case for this department to be self-contained. The essence in treating trauma is urgency; and great difficulties arise if the accident case has to compete with set lists of " cold surgery ". Similarly there are special requirements, such as blood transfusion appropriate for different degrees of urgency, and bacteriological and biochemical services similarly keyed to the precise needs of these patients.

Some of the criticism of an accident " centre " perhaps derives from its being looked upon as a Big Brother establishment, perhaps newly created; but it should be regarded as a development of an existing efficient accident department, which can then support others as required with suitable staff and facilities for research and teaching.

J. P. BULL
D. MACG. JACKSON
P. S. LONDON.

Birmingham Accident Hospital, Birmingham.

EFFECTS OF COD-LIVER OIL

SIR,—It would be unfortunate if the excellent demonstration by Dr. Kingsbury and his colleagues (April 8) of the hypocholesterolæmic effect of cod-liver oil were to lead to its indiscriminate use for the prevention of coronary atherosclerosis. Their evidence tends to suggest that the hypocholesterolæmic effect increases with the size of the dose; and it might be argued that doses larger than they gave should be even more effective. I cannot express any views as to the possibility of side-effects from high doses of cod-liver oil among adults; but I believe that the acceptance of this argument by parents anxious for the continuing welfare of their children in the years ahead may conceivably lead to serious consequences.

A causal role has been attributed to vitamin D in idiopathic hypercalcæmia of infancy; and since the amounts of vitamin D_2 in the welfare foods were reduced in 1957 its incidence and severity appear to have declined.[1] Vitamin D_2 has been incriminated rather than vitamin D_3; the former has undoubtedly provided by far the greater part of the vitamin-D intake of children in recent years. Nevertheless vitamin D_3 and cod-liver oil have also been found to cause poisoning in children,[2] and may moreover cause heart lesions. Myocardial lesions, and electrocardiographic signs suggestive of them, have been attributed to cod-liver oil medication in early childhood [3–5]; and from my own unpublished observations it is clear that in young rabbits calcinotic lesions of the myocardium, and lesions of the media of the aorta, as well as renal medullary calcinosis can be produced by either type of vitamin D. In certain instances the amounts of cod-liver oil or of vitamin D_3 per unit of body-weight have been exceptionally large; but individual hypersensitivity to vitamin D_2 has now been postulated in idiopathic hypercalcæmia,[6–8] and it would be unsafe to assume that individual hypersensitivity to vitamin D_3 cannot also occur.

Following closely upon the publication of the work of Dr. Kingsbury's group, one commercial firm has distributed a pamphlet which not only extols the merits of cod-liver oil, but urges its use as a dietary supplement without making any reference to the possiblity of harmful effects. We have only recently recognised and largely overcome the harmful effects associated with excessive dosage of vitamin D in preventing rickets; and it would be a matter for concern if unrestrained and lengthy treatment with cod-liver oil for the prevention of coronary atherosclerosis were now to be accepted. The substance is potentially toxic, and undesirable effects might be expected from lengthy treatment at high dosage, particularly if that treatment were to begin in early childhood.

Royal Hospital for Sick Children, Glasgow.

ERIC N. COLEMAN.

1. Creery, R. D. G. *Lancet*, April 15, 1961, p. 832.
2. Thatcher, L. *ibid.* 1936, i, 20.
3. Malmberg, N. *Acta pædiat., Stockh.* 1928, **8**, 364.
4. Jundell, I., Stenstrom, N. *ibid.* 1931, **12**, 113.
5. Uhse, W. *Jb. Kinderheilk.* 1935, **144**, 63.
6. Lowe, K. G., Henderson, J. L., Park, W. W., McGreal, D. A. *Lancet*, 1954, ii, 101.
7. Carter, R. E. B., Dent, C. E., Fowler, D. I., Harper, C. M. *Arch. Dis. Childh.* 1955, **30**, 399.
8. Fellers, F. X., Schwartz, R. *New Engl. J. Med.* 1958, **259**, 1050.

WHO IS DELIVERED?

SIR,—I am grateful to your distinguished correspondents, Mr. Vartan and Mr. Arnold Walker (April 15), for their support on the question of how the word " delivered " is correctly used in midwifery.

I think we are all agreed that the baby is born and the mother is delivered, but evidently the Ministry of Health does not share this view. In their recent publication, Human Relations in Obstetrics, we read, alas, on page 1, " Some mothers complain that they are contradicted when they say they are about to deliver their baby ", and again on page 4, " The delivery of the baby is, to the mother, the culmination of a prolonged waiting period ".

I fear, however, we are tilting at windmills.

Exeter. P. M. G. RUSSELL.

DUCT PAPILLOMA OF THE BREAST

SIR,—Your annotation (April 15) raises some questions of great interest and importance to surgeon and diagnostic pathologist alike.

Perhaps some of the difficulty in answering the question which you posed is due to absence of generally accepted nomenclature for the various pathological changes in the breast. There are 4 conditions in which papillary proliferation occurs within the mammary-duct system—i.e., papillary epitheliosis, solitary papilloma (especially in the lactiferous sinuses), papillomatosis within one or more duct systems, and papillary adenocarcinoma of the breast.

I believe that nearly all duct papillomas are benign, and do not call for radical surgery. It is important to realise that all red and brown nipple discharges do not contain blood, and must not be taken as evidence of papilloma without cytological examination. All pathologists have had occasion to examine breasts removed because of nipple discharge, in which no papilloma could be demonstrated despite the most careful search. Such breasts may be the seat of mammary-duct ectasia—a condition not as widely recognised as it deserves to be, and one in which nipple discharge is fairly common.

All nipple discharges should be examined cytologically; if the maximum information is to be gained from such examination, smears must be properly made, appropriately fixed while still wet, and suitably stained. It is an advantage to use both Papanicolaou's method, and also hæmalum and eosin staining after Schaudinn fixation. In cases of duct papilloma presenting with discharge, red blood-cells, tumour-derived epithelial cells (either singly or in clumps), and sometimes siderophages are observed. Similar appearances may be seen in advanced intraduct epitheliosis or carcinoma; it is sometimes possible to assess the degree of dedifferentiation of the epithelial cells. More important, however, is the possibility of recognising that the discharge may be derived from duct ectasia; in this condition the characteristic finding is the presence of numerous large foamy macrophages (colostrum corpuscles), and of sudanophilic lipid. Red blood-cells and unaltered epithelial cells are rarely present. If there are no facilities for full cytological examination, much useful information may be obtained by examining a simple wet film of the discharge.

When discharge is accompanied by a lump in the breast there is no clinical problem, and the lump must be excised for immediate or formal histological examination; the surgeon is

guided by the findings. If there is a discharge of duct-papilloma type which can be localised to one area of the breast the surgeon may lay open the affected duct until the tumour is displayed. Local resection is the treatment of choice in younger women where histological evidence of aberration or invasion is absent; mutilating mastectomy should be avoided unless widespread involvement of the duct system is suspected.

When the discharge cannot be localised, the possibility of mammary-duct ectasia should be considered, and repeated cytological examination of the discharge should be undertaken. If neither red blood-cells nor unaltered epithelial cells can be detected in several specimens, and no mass can be felt, then mastectomy does not seem justified.

University Pathology Department,
Western Infirmary,
Glasgow.

A. T. SANDISON.

ACUTE OSTEOMYELITIS TREATED WITH METHICILLIN

SIR,—We have had 2 interesting cases of acute osteomyelitis recently.

CASE 1.—A lad of 15 became semicomatose, with muttering delirium and a high fever. There were bilateral effusions into the knee-joints. He did not complain of bone pain. The diagnosis remained in doubt until blood-culture yielded *Staphylococcus aureus*. Because he was obviously gravely ill methicillin (' Celbenin ') was given after initial treatment with penicillin, streptomycin, and sulphadiazine had been ineffective. He slowly responded, bilateral tibial abscesses were drained, and eventually he recovered completely.

CASE 2.—A man of 33 was admitted irrational and semicomatose, with a pyrexia of 103°F. Again the diagnosis was in doubt until blood-culture yielded *Staph. aureus*; and chloramphenicol was prescribed. In this case though methicillin was recommended it could not be given until three days after admission. His temperature then fell, but he remained irrational, and did not recover. At necropsy osteomyelitis of the right humerus, septic infarcts of the brain, acute endocarditis, and abscesses of the kidney were observed.

It may be significant that in both cases the organism subsequently proved sensitive in vitro to penicillin, tetracyline, erythromycin, and chloramphenicol; but in vivo neither penicillin in case 1 nor chloramphenicol in case 2 had any appreciable effect. It seems that methicillin should be given at once in overwhelming infection when *Staph. aureus* is isolated on blood-culture. The importance of blood-culture is obvious; and the medical bacteriologist should give prompt advice as soon as he has the necessary information.

My thanks are due to my clinical colleagues for access to the case-notes.

Department of Pathology,
The Royal Hospital,
Wolverhampton.

C. H. L. HOWELLS.

EXTERNAL CARDIAC MASSAGE

SIR,—It seems to me that your correspondents are referring to two quite distinct and different procedures. The first is the true " external cardiac massage " combined with artificial respiration, as described by Rainer and Bullough,[1] and modified by Kouwenhoven et al.[2] The second procedure is probably analogous to the " gentle flick " to the misbehaving heart, mentioned by Mr. Weale (Jan. 21), and it appears probable, despite the implied vigour of Dr. Healy's blow to the epigastrium (March 4), that his patient was subjected to this method.

A recent case of mine would also appear to fall into the latter category. A man of 56 had sustained a major anterior cardiac infarction at 3 A.M. He was comfortably installed in hospital, and was reasonably well, in sinus rhythm, but with low blood-pressure (80/60). At 3 P.M. he suddenly collapsed, and I saw him about two minutes later. He was then pale and livid, and apnœic, and no heart-sounds were audible. I sent sister for a scalpel, and at that moment Mr. Molloy's original letter (Jan. 7) came to my mind.

I gave the patient 3 rapid, light, but incisive blows to the precordium with my fist. Faint and irregular heart-sounds immediately became audible, and conventional artificial respiration was started. After three minutes an attempt was made to insert an airway. He started to gag and vomited a few ounces of clear fluid, and almost immediately regained consciousness, though he was confused. An electrocardiograph, taken thirty minutes from the onset, was similar to the original tracing, apart from the presence of definite sinus tachycardia. Next day he developed the susurrus of pericardial friction (possibly iatrogenic), and paroxysmal atrial fibrillation, which was rectified with quinidine. One week later his condition was satisfactory.

In retrospect I can certainly say that the blows were not heavy enough to depress the thoracic cage sufficiently to empty the heart.

Bulawayo,
Southern Rhodesia.

J. CHARLES SHEE.

MYOGLOBINURIA

SIR,—Yet another group of patients might be added to those you described in your leading article (April 1) with Haff disease, obvious muscle trauma, or idiopathic paroxysmal myoglobinuria.

As first noted by Fahlgren et al.,[1] acute, debilitating, and even fatal myonecrosis, myoglobinuria, and renal failure may accompany alcoholic excess and fatty liver. We have recently studied a patient with this syndrome. Since muscle weakness, oliguria, and dark urine are common findings in patients with the fatty cirrhotic liver of alcoholism, only a careful history and examination of the urine will lead to the proper diagnosis. Unfortunately, the relationship between alcoholism, liver-disease, and myoglobinuria remains obscure.

Massachusetts General Hospital,
Boston.

WILLIAM A. TISDALE.

ESSENTIAL-FATTY-ACID CONTENT OF HENS' EGGS

SIR,—Coppock et al. (Jan. 14) recently drew attention to the similarity in essential-fatty-acid (E.F.A.) content of eggs from free-ranging and battery housed hens. Gresham and Howard (Feb. 4) later doubted the importance claimed for E.F.A. in preventing arterial disease.

But Dr. Sinclair (Jan. 28 and Feb. 11) continues to prefer free-range to battery eggs in his diet on the ground of supposed differences in their atherogenic properties. He quotes (Jan. 28) an experiment in support of this preference in which sudanophilic material was found in the aortæ of day-old chicks hatched from eggs of battery hens, but not in those hatched from those of free-range hens.

Unfortunately no details were given of the number of chicks or of the staining technique used. We have felt it desirable to repeat Dr. Sinclair's experiment in an attempt to assess the differences between these two types of aorta. In fact our experiments have failed to disclose any differences whatsoever.

Twenty-four fertile eggs from artificially inseminated battery birds (Rhode Island Red × Light Sussex, from Houghton Poultry Research Station, Huntingdon) and a similar sample of fertile eggs of free-range birds (pure Light Sussex—birds on grass at a local farm) were incubated separately in two ' Curfew ' electric observation incubators.

1. Rainer, E. H., Bullough, J. *Brit. med. J.* 1957, ii, 1024.
2. Kouwenhoven, W. B., June, J. R., Knickerbocker, G. G. *J. Amer. med. Ass.* 1960, **173**, 1064.

1. Fahlgren, H., Hed, R., Lundmark, C. *Acta med. scand.* 1957, **158**, 405.

The eggs of both groups were turned by hand three times daily up to the 18th day, and after 21 days an almost equal hatch was obtained from the battery and free-range groups respectively.

The experiment was so organised that the chicks from both groups hatched within a 24-hour period. A random sample of 11 one-day-old chicks was taken from each group for necropsy. Chicks were examined in pairs, one from each group; and the pair was killed by ether anæsthesia. The aortæ were exposed and opened in situ; they were then removed and fixed in buffered 10% formol-saline for two hours. After fixation aortæ were stained in pairs for 15 min. in a saturated solution of Oil Red O in equal parts of acetone and 70% ethanol. The preparations were then differentiated for $1^1/_2$ min. in 90% ethanol, rinsed in formol-saline, and examined under a dissecting microscope at a magnification of 35.

The paraaortic adipose tissue stained bright red, and a few red droplets were visible beneath the adventitia in both groups. No intimal sudanophilia was detected in either group. We found, therefore, nothing to support Dr. Sinclair's suggestion that battery hens' eggs are nutritionally inferior to those from free-range birds as determined by the aortic development of the day-old chick.

Further work on gas-liquid chromatographic analysis of the lipids of these two types of aorta will be published later.

Spillers Limited, Technological Research Station, Cambridge.
J. B. M. COPPOCK
N. W. R. DANIELS.

Department of Pathology, Cambridge.
G. A. GRESHAM
A. N. HOWARD.

USELESS QUARANTINE?

SIR,—It was a pleasure to read the common-sense views expressed by Colonel H. Foster in his letter (April 1). I am sure that he is right in advocating considerable relaxation in quarantine restrictions applied to the common infectious diseases. I agree that far too many children are excluded from school quite unnecessarily, and for too long.

For the past eleven years in this city we have not routinely excluded contacts in any of the common infectious diseases such as scarlet fever, chickenpox, measles, whooping-cough, rubella, and mumps; and four years ago Sonne dysentery was added to this list. Very occasionally individual contacts may be excluded on the advice of the general practitioner or the school medical officer, but these are the exception rather than the rule. I have at no time had cause to regret this more liberal policy.

Oxford.
JOHN F. WARIN
Medical Officer of Health.

"A DEPARTURE FROM NORMAL PRACTICE"

SIR,—The remarks of Dr. Tredgold and Dr. Soddy (March 25) about the case of Landau *v.* Werner are apposite and, as they say, the outcome in this case is of great concern to psychiatrists and general practitioners. And there are other aspects which they did not mention which are very disturbing:

(1) Since letters written many years earlier were admitted in evidence, the case is a lesson to psychiatrists and practitioners who might not keep letters they receive from patients. If such letters are to be admissible in evidence it will mean that they will have to be kept for many years and probably until the patients die.

(2) The only psychiatric evidence which seemed to confirm the contentions of the prosecution was based on one psychiatric interview with the patient eight years previously. Would it not be an advantage if psychiatrists appearing for the parties were to examine any mentally ill patient within a short period before the case is heard?

(3) The delay in bringing the case was evidently responsible in part for the heavy damages, and this is a warning to psychiatrists and other doctors to inform their defence societies if they seriously suspect that a patient may sooner or later take legal action against them.

(4) Some of Miss Landau's evidence was accepted as true and some as untrue. Do the legal authorities understand the full significance and implications of legal action taken by patients with mental illness against their doctors, and do they realise the difficulties they are likely to meet in the future in dealing with a case of amorous or litigious paranoia, since this is the type of patient who may well take action against the doctor?

London, W.1.
DONALD BLAIR.

FŒTAL ABNORMALITY

SIR,—In your account of April 8 of the conference on this subject you reported that I had observed that "an abnormal facies was not always associated with a severe renal lesion in the fœtus, even if the pregnancy had been complicated by hydramnios". What I said, in fact, was that Potter's facies could be found, not only in bilateral renal agenesis, but also in association with other congenital abnormalities of the urinary tract, including urethral obstruction by mucosal folds and severe phimosis. In all the cases observed, there had been oligohydramnios or anhydramnios, which might possibly be the decisive factor in the causation of the abnormal facial features.

I am also reported to have said that "catheterisation of the infant's œsophagus was useful when hydramnios was found in pregnancy" (and no external malformation apparent at birth). This is correct, but the point of my contribution to the discussion was, that even where the œsophagus had been found to be patent, one could not exclude the possibility of some malformation causing outside pressure on the upper alimentary tract. A relevant observation was referred to: a case of severe hydramnios with no external deformity of the infant; catheterisation revealed patency of the œsophagus. At necropsy, however, a persistent truncus arteriosus (grade 4) was found with a very high and wide aortic arch, closely apposed to the œsophagus and likely to interfere with deglutition.

Department of Pathology, Birmingham Maternity Hospital.
H. G. KOHLER.

TECHNIQUE OF CRANIOTOMY

SIR,—I wonder how many neurosurgeons still avoid making burr-holes in the midline when performing a craniotomy near it? Some surgeons mark the midline meticulously with a scratch or bradawl marks on the bone, in order to avoid damage to the sagittal sinus.

In fact the dura over the sinus is tougher and less adherent to the bone than it is $^1/_2$ in. on either side of it, where large cortical veins enter the layers of the dura. A line of burr-holes and Gigli-saw cuts linking them can be made almost bloodlessly, by keeping strictly over the sinus itself, without danger of calamity, and with better access to the region of the falx. If angiographic details of the cortical veins are available, these also can be avoided in making the coronal saw cuts; even then they will occasionally ooze when the bone-flap is lifted, but this bleeding is easily stopped without sacrificing a vein, which is sometimes necessary when it has been torn by guide or saw.

Brook General Hospital, London, S.E.18.
JOHN R. GIBBS.

RESPIRATORY COLLAPSE DUE TO PLASTIC SPRAY DRESSING

SIR,—An unusual incident happened to a five-month-old baby on whom I operated for ileocæcal intussusception.

After the operation was finished, while the anæsthetist was aspirating the baby, who was now fully conscious, I decided to dress the right paramedian incision with 'Aerofilm' (Laboratoires

Fournier, Dijon), a spray-on plastic wound dressing like 'Nobecutane'. Immediately after I finished spraying, the baby became unconscious, apnœic, and cyanosed, and only regained consciousness after being given oxygen for ten minutes.

Both the anæsthetist and I are convinced that this was due to the spray, which contains acetone and ethyl acetate as solvents. It is noteworthy that while actually spraying we covered the baby's face, and it was only when we fanned the sprayed surface that the baby's face was not shielded.

I do not know if anything similar has already been reported; but I think that the possibility should be kept in mind.

King Paul's General Hospital, Athens. N. J. GEORGIADIS.

ATYPICAL TURNER SYNDROME

SIR,—We wish to report our preliminary findings in an apparent example of gonadal dysgenesis with stunted growth. The case is of particular interest for two reasons: (i) chromosome analysis is suggestive of a previously undescribed mosaicism, and (ii) in smear preparations of buccal mucosa the number of nuclei with a well-defined sex-chromatin body is very high.

A $14^1/_2$-year-old girl of small stature (height 44 in.) has some signs of puberty, but has progressed slowly. Pubic and axillary hair remains scanty, and the breasts are poorly developed. There has been no menarche. Œstrogens are not demonstrable in her urine, but 17-ketosteroid and gonadotrophin excretion are normal. Her bone age is normal. She has no webbing of the neck, cubitus valgus, coarctation of the aorta, or hypertension.

We believe that her clinical condition is more in keeping with gonadal dysgenesis than with hypopituitarism.

In buccal smear preparations 136 (91%) of the 150 cells examined each showed 1 large sex-chromatin body. Sex chromatin was absent from the remaining 14 cells. The number of suitable nuclei showing a sex-chromatin body in normal females is found, in this laboratory, to be between 50% and 80%.

Leucocytes derived from peripheral blood were cultured for three days and prepared for chromosome analysis. Two separate cultures were prepared. In each culture the chromosomes in 65 cells were counted. 117 cells contained 46 chromosomes, and 13 (10%) contained 45. 7 of the cells with 45 chromosomes were derived from one culture, and 6 from the other. In 20 cells with 46 chromosomes the chromosomes were analysed in detail. In each of these there was an extra chromosome in group number 3 (Denver system) and one less than is normal in group 6–12+X (fig. 1). The missing chromosome is believed to be an X. Precise identification of the remaining X chromosome was difficult. In none of the 13 cells with 45 chromosomes were 3 no. 3 chromosomes apparent. The "extra" chromosome appears to be absent from these cells. In all 13 there were quite definitely only 15 chromosomes in the 6–12+X group (fig. 2). The missing chromosome is again presumed to be an X. This case will be more fully reported later.

The mosaicism described above in each of two separate cultures probably indicates that two different cell types are present in the patient; although the frequencies observed in culture are not necessarily those present in the body.

3 patients recently described by Fraccaro et al.[1] under the heading of gonadal dysgenesis apparently have similar abnormalities to those we describe in the cells with 46 chromosomes. The interpretation most attractive to Fraccaro et al. is that the abnormal chromosome (one of group number 3) is an "isochromosome" for the long arm of one of the X chromosomes. Observations on the morphology of the number 3 and presumed X chromosomes in our case support this hypothesis. The cells with 46 chromosomes are then effectively trisomic for the long arm, and monosomic for the short arm of X. Two of the long arms (those on the abnormal chromosome of number 3) are genetically identical. It may be significant that in buccal smear preparations from our patient the percentage of cells with a sex-chromatin body was greater than the usually accepted normal upper limit. The cells with only

1. Fraccaro, M., Ikkos, D., Lindsten, J., Luft, R., Kaijser, K. *Lancet*, 1960, ii, 1144.

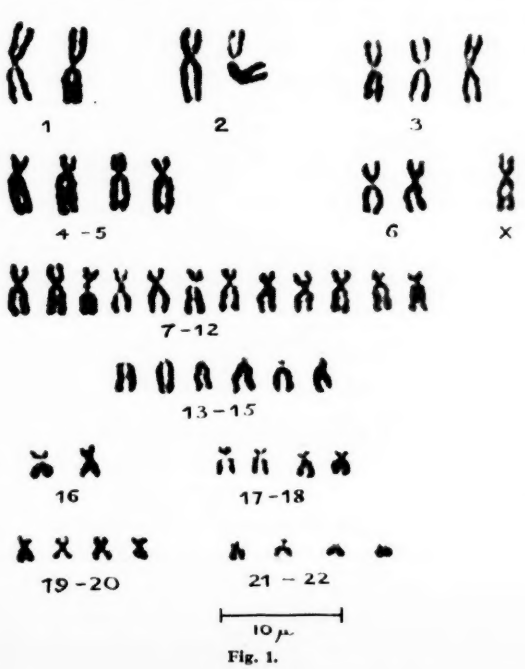

Fig. 1.

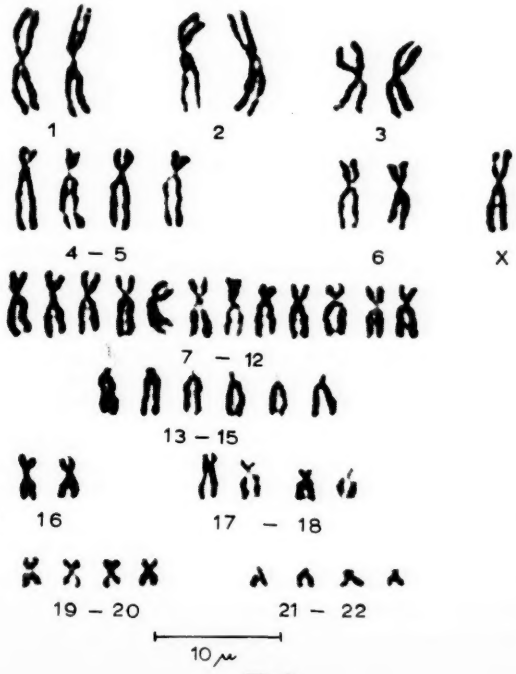

Fig. 2.

45 chromosomes are presumably monosomic for both long and short arms of X.

The chromosomal irregularities attributed to this patient may have arisen at first cleavage division in a zygote with, initially, a normal (44A+2X) chromosome complement. Transverse division of the centromere of an X chromosome might be expected to give rise to a pair of isochromosomes: one of which (that involving the chromatids of the short arm) may lag at anaphase and fail to be included in either daughter nucleus. Such a faulty division, with subsequent loss of one of the products, would result in a 46/45 mosaic. The cells with 46 chromosomes would contain one normal X and an isochromosome for the long arm of its homologue, and the cells with 45 chromosomes would contain only 1 (normal) X chromosome. Other mechanisms are, of course, possible but the one outlined above seems the simplest.

This research is supported by a grant from the Medical Research Council.

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Sheffield.

C. E. BLANK
R. R. GORDON
AUDREY BISHOP.

SIGNIFICANCE OF PALATAL PETECHIÆ IN INFECTIOUS FEVERS

SIR,—Petechiæ on the palate, especially in febrile disease, have been much discussed. Their presence at the junction of the hard and soft palate has been considered almost pathognomonic of glandular fever; and more widespread palatal petechiæ have been described in other infectious fevers.

We have recently seen petechiæ at the junction of the hard and soft palate not only in glandular fever in a child with a typical blood-picture and positive Paul-Bunnell test, but also in a young adult with fever due to A.P.C. virus, and in an old lady with acute pharyngitis.

In our opinion this sign is quite non-specific and is probably attributable to the following:

(1) Increased capillary fragility due to congestion of the fauces and posterior palate, often present, and probably associated in many cases with widespread viræmia, a well-known cause of capillary damage.

(2) Further mechanical trauma to the capillaries by cough and frequent clearing of the throat because of faucial irritation.

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SIDNEY SHAW
ROSALINDE HURLEY.

COAGULATION INHIBITOR REVEALED BY THROMBOTEST

SIR,—The thrombotest of Owren [1] has been widely discussed in your columns [2]; and our investigations of a patient with a lengthened thrombotest-time, but with all other coagulation-test results within normal limits, may therefore be of interest.

A 60-year-old woman had undergone a partial gastrectomy at the age of 52 for peptic ulcer. No signs of a hæmorrhagic diathesis have ever been demonstrated; and there is no family history of a tendency to bleed. She was now admitted to an orthopædic department on account of intermittent claudication due to arteriosclerosis. Vascular surgery combined with anticoagulant therapy was considered; so the coagulability of her blood was estimated by thrombotest on her citrated plasma. This was the routine method in the department for controlling anticoagulant therapy. By repeated estimations with different batches of thrombotest reagents and different blood-samples values were 30–45% of normal. On menaphthone ('Menadione') given intramuscularly for several days no improvement was noted. The patient was transferred to a medical department for further investigations. No evidence of liver-disease was found. Apart from arteriosclerosis and iron deficiency (presumably due to an inadequate diet) no disease was observed. The anæmia responded well to iron therapy.

The thrombotest was performed several times on blood and plasma in two different laboratories; values were 45–50%. Results of Owren's prothrombin-proconvertin test, Quick's one-stage prothrombin test, the bleeding-time, Lee White's clotting-time, platelet-count, recalcification-time in diluted and undiluted citrated plasma, cephalin-time, thrombin-generation test, and thromboplastin activation test (Astrup and Ollendorff) were all within normal limits.

Different test-substrates were then added to the patient's diluted plasma in the thrombotest. A diluted, normal plasma was used as a control (see table).

The total volume in all the experiments was 0·6 ml. All tests were performed in duplicate. Besides the addition of test-substrates, the thrombotest was performed on diluted plasma.[1]

It will be seen from experiments 3 and 6 that the defect in the patient's plasma was only corrected by serum. This serum was "aged" as, after coagulation in clean glass tubes, it was kept for 2 hours at 37°C, and then stored for at least 18 hours at 4°C. It is remarkable that the patient's own "aged" serum had the same corrective effect as normal serum. That the shortening of the clotting-time is not due only to the clot-promoting effect of serum is evident from comparing the results with those obtained with the control plasma. Normal plasma diluted to 20% did not correct the defects in the patient's plasma (experiment 9). Experiment 10 demonstrates that the patient's plasma had an inhibitory influence on normal plasma. This influence is not a dilution effect alone, as in the more diluted normal plasma in experiment 11 the coagulation-time was shorter.

Thus it has been possible to demonstrate by the thrombotest an in-vitro clotting defect which other tests did not reveal. The defect seems to be due to an inhibitor in the patient's plasma which can be neutralised by a substance formed both in normal blood and in the patient's blood during clotting and present in "aged" sera. The clinical significance of this observation is unknown.

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P. OLLENDORFF.

1. Owren, P. A. *Lancet*, 1959, ii, 754.
2. See *ibid.*, 1960, i, 63, 224, 229, 383, 436, 550, 600; *ibid.* ii, 553, 931, 1115; *ibid.* March 11, 1961, p. 557.

RESULTS OF THROMBOTEST

—	Experiment no.										
	1	2	3	4	5	6	7	8	9	10	11
Diluted normal plasma	..	0·1	..	..	..	..	0·095	0·095	0·005	0·066	0·05
Diluted patient's plasma	0·1	..	0·095	0·095	0·095	0·095	..	..	0·095	0·033	..
Normal serum	..	..	0·005	..	..	..	0·005	..	..	..	..
Patient's serum	..	..	..	..	..	0·005	..	0·005	..	..	..
Adsorbed heated normal serum	..	..	..	0·005	..	..	..	..	..	..	..
Adsorbed bovine plasma	..	..	..	..	0·005	..	..	..	..	..	..
Thrombotest reagent	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5	0·5
Physiological saline	..	..	..	..	..	..	..	..	..	..	0·05
Coagulation-time (sec.)	50	36	36	49	50	34	34	34	46	44	42·5

Quantities in ml.

NEEDS AND BEDS

SIR,—May we comment on the reasons put forward by Dr. Waind (April 22) for the differences between the assessments of clinical need for admission to hospital made by Crombie and Cross,[1] Mackintosh et al. [2] in Birmingham, and ourselves at Barrow? [3]

Dr. Waind is right when he says such assessments are purely subjective because satisfactory criteria have not been established. In the Barrow survey we did our imperfect best to make clear the criteria we adopted:

"This assessment is admittedly subjective . . . it was assumed that general practitioners were willing, aided by the domiciliary services of the Local Authority, to undertake home care. It was assumed also the Outpatient departments had all the diagnostic facilities readily available. In fact, of course, none of these conditions applied." (p. 82.)

We were dealing with an unreal situation and said so. We then (pp. 84–87) gave some case-studies showing the general nature of the criteria we used.

Nevertheless the assessments of clinical need remained subjective; but it is not without significance that Dr. Crombie, a general practitioner, and Dr. Logan, associated with general practice through Darbishire House Health Centre, find a higher proportion of clinically unnecessary admissions than a group of hospital consultants and a team of research-workers engaged in the teaching of public-health administration. Clearly an important factor is the attitude to the role of the G.P. Those who believe the family doctor still has a place in clinical medicine will take a different view of the need for hospital admissions than those who do not. Dr. Crombie presumably made his assessment by asking whether, had the patient been his, he would have referred the case to hospital, knowing at first hand the possibilities of general practice today. We took the same attitude and found similar results. We fully recognise that these methods are crude; but no great harm will be done if those who carry out ostensibly comparable surveys are equally careful to indicate, so far as they can, their own assumptions and prejudices.

Dr. Waind's final criticism, that these assessments are retrospective and may therefore miss what had been an urgent clinical situation, is valid but would not apply to all the cases involved. Dr. Waind would agree, we hope, that acceptable methods can be developed in these complex fields only on the basis of unsuccessful attempts.

Finally, Dr. Waind may inadvertently have given an impression which does less than justice to himself and his colleagues in Barrow, for without their full cooperation at all stages, particularly in discussing the cases at the bedside and commenting on our draft report and results, the survey would not have been possible.

Department of Social and Preventive Medicine, University of Manchester.

GORDON FORSYTH
R. F. L. LOGAN.

SIR,—In their article of April 22, on the demand on children's hospitals, Professor Illingworth and Professor Knowelden refer to some remarks of mine made in 1956.[4] The intention of my discussion then was to describe how, given only a relatively small number of children's hospital beds, these could be made to do a surprisingly large amount of work, *whenever they could be intensively employed*. The absolute number of beds is less important than that they should be concentrated in a properly staffed and properly equipped children's unit.

As Professor Illingworth and Professor Knowelden have now shown, there has been a steady increase in the work done by children's hospitals throughout the country over the past 10 years. Undoubtedly a similar increase would also be apparent in pædiatric units in general hospitals, to judge by our own experience. Here the number of pædiatric admissions is now running at a level 38% above that in the years before 1956, though the local factors (which I then mentioned as favouring a low rate of child admissions) have persisted. Three causes have been responsible for this increased work in Cambridge, as no doubt elsewhere:

(1) The rise in the birth-rate (about 12% more babies are being born in Cambridgeshire now than 5 years ago).

(2) The ever-widening range of diagnosis and treatment.

(3) The closing down of the smaller children's wards in outlying hospitals, leaving the main children's unit to take over their work. Such transfer of work from several scattered units to a single centre (though more often brought about by the impossibility of staffing small units than as a matter of accepted policy) is entirely to be welcomed, for as you, Sir, argued in a leader,[5] "from the medical standpoint, only the large pædiatric unit can be fully efficient". Small units of 8–10 children's beds, which the Platt Report on children in hospital [6] regarded with some favour, in my experience have proved neither an effective nor an economical way to care for children in hospital.

In order to foster good pædiatrics in this country, therefore, we "need to build up, in each region, a relatively small number of big pædiatric units, fully staffed and fully equipped —with special attention to any children's hospitals . . .".[2] The facts provided by Professor Illingworth and Professor Knowelden for children's hospitals, like those which have been given by Taylor and Davison [7] for the Newcastle area, thus underline the vital need for pædiatrics to be accorded its full share of new hospital building.

Addenbrooke's Hospital, Cambridge.

DOUGLAS GAIRDNER.

McARDLE'S SYNDROME

SIR,—The fascinating story (April 22, p. 872) of the investigations which led to the link up between McArdle's syndrome and glycogen-storage disease is a striking testimony to the value of chemical techniques intelligently and knowledgeably applied. A case recently reported by us [8] shows, however, that anatomical studies can on occasion be equally valuable.

The patient was a young woman who had apparently suffered from a myopathy for 10 years. At no time did she complain of cramps, pain, or stiffness in the muscles as in the syndrome described by McArdle. Nevertheless muscle biopsy showed a substance with the staining reactions of glycogen in the muscle-fibres giving them the appearance seen in Schmid and Mahler's [9] case of the syndrome. When our patient died a year after biopsy we were able to show changes in the liver and heart similar to those seen in the cardiomegalic form of glycogen-storage disease.

It is not yet known whether the cases of McArdle's syndrome reported so far will show changes in the liver and heart, but our case emphasises the importance of looking for them. 16 other cases of glycogen-storage disease affecting muscle have been described, but ours was the first adult case. It is probable that more than one enzymatic defect can cause accumulation of glycogen in the muscle-fibres, and it is important that in future cases attempts should be made not only to assess enzymatic activity but also to determine the molecular structure of the glycogen.

The possibility suggested in your annotation of at least symptomatic improvement with treatment is an additional reason for making every effort to recognise the disease. We pointed out in our report that a material with the staining reaction of a polysaccharide was present in the renal tubules, and it may in future be worth examining the urine for such substances. Most important, however, is our patient's history,

1. Crombie, D. L., Cross, K. W. *Med. Pr.* 1959, **242**, 316.
2. Mackintosh, J. M., McKeown, T., Garratt, F. N. *Lancet*, April 15, 1961, p. 815.
3. Forsyth, G., Logan, R. F. L. The Demand for Medical Care. London, 1961.
4. Gairdner, D. *Proc. R. Soc. Med.* 1956, **49**, 974.
5. *Lancet*, 1958, ii, 197.
6. The Welfare of Children in Hospital; p. 9. H.M. Stationery Office, 1959.
7. Taylor, M., Davison, G. *Lancet*, 1959, ii, 453.
8. Holmes, J. MacD., Houghton, C. R., Woolf, A. L. *J. Neurol. Neurosurg. Psychiat.* 1960, **23**, 302.
9. Schmid, R., Mahler, R. *J. clin. Invest.* 1959, **38**, 2044.

which suggests that increased recognition of this rare but important disease will necessitate a broadening of our concepts of its mode of presentation.

J. MACD. HOLMES
Smethwick. A. L. WOOLF.

SPIRONOLACTONE THERAPY IN HYPOKALÆMIA

SIR,—A 6-year-old boy has been under our care since the age of 18 months because of dwarfism and episodes of severe dehydration with vomiting.

Constant findings have been diminished skin turgor, polyuria with polydipsia and disturbance of blood-electrolytes: hypokalæmia (1·9–2·9 mEq. per litre); hypochloræmia (70–90 mEq. per litre); alkalosis: arterial pH 7·54, and bicarbonate 30–40 mEq. per litre; serum-sodium values, when hydration was maximum, 140 mEq. per litre, during dehydration approximately 133 mEq. per litre. His urine was alkaline (pH 7·6–8·0) with a low specific gravity.

Fæcal loss and potassium-losing nephritis were excluded as a cause of the hypokalæmia.

Loading with potassium chloride, potassium citrate, or a combination of potassium chloride and ammonium chloride did not influence the hypokalæmia. Acetazolamide (' Diamox ') in doses up to 70 mg. per day did not affect the alkalosis or the already high bicarbonate excretion in the urine.

This combination of findings might suggest a hormonal disturbance, such as excessive secretion of aldosterone, deoxycortone (11-desoxycorticosterone), or corticosterone.

Primary hyperaldosteronism was ruled out as a cause since: (1) the aldosterone values fell from 37·4 μg. and 28·2 μg. per day to a normal level of 5 μg. per day (estimations performed by Dr. A. H. Gowenlock, Manchester) when the sodium intake was increased from 20 to 68 mEq. per day; (2) there was no hypertension; (3) the skin turgor was always diminished; (4) the sodium/potassium ratio in saliva and sweat was normal.

The possibility of high production of deoxycortone was excluded by a detailed urinary analysis by Dr. R. Neher (Ciba, Basle). Urinary corticosterone was found to be increased.

On the hypothesis of impaired hydroxylation of the corticosteroids at C17—analogous to the adrenogenital syndrome—prednisone was given. But the patient did not improve on prednisone; in fact he developed a negative sodium and potassium balance, and his general condition deteriorated. Increasing hypotonia, lassitude, anorexia, and vomiting developed. Transient hepatomegaly was observed: thymol turbidity was 7·4 units. (Serum-bilirubin was not increased, serum-protein electrophoresis pattern was normal.) The patient's clinical condition did not warrant a further trial with prednisone at this time.

In an attempt to block the action of corticosterone on the sodium/potassium exchange in the renal tubule, spironolactone (' Aldactone ', ' SC 9420 ', Searle), which is known to antagonise this effect, was given in three short trials of two consecutive days in a dosage of 100 mg., 600 mg., and 800 mg. per day, respectively. In the first trial no effect was seen. In the other trials there was potassium retention and sodium diuresis, increased serum-chloride, and slight improvement in arterial pH. Spironolactone had to be discontinued during the third trial, because the patient vomited persistently.

Because of its possible therapeutic effect spironolactone was again tried, but in a lower dosage over a longer period; the dose was cautiously increased (by 50 mg. every 4 days). Initially doses of 50 mg. a day were given. The diet at this time was fixed and its sodium, potassium, and chloride content was known. Additional potassium chloride and sodium chloride were given. A daily determination of the electrolytes in the 24-hour urine specimen made it possible to be aware of changes in the electrolyte balance before a sudden change in blood-electrolytes resulted. Since spironolactone produced a sodium diuresis, the intake of sodium had to be adapted to avoid sodium depletion. The following combination was found to be successful: sodium, 140 mEq.; potassium, 78 mEq.; spironolactone, 300 mg. per day. Since then the patient has gradually improved; and the serum-chemistry is as follows (mEq. per litre): K^+ 3·5—4; Na^+ approximately 140; Cl' 90–100; HCO_3' 22–29; the arterial pH was 7·45.

An adrenal tumour is unlikely since there is no renal displacement on intravenous pyelography and symptoms have been present for six years. Supporting evidence comes from the patient's brother (not under our care), who is said to have a similar illness.

We conclude that this patient has a rare familial disease, and the electrolyte disturbance responds to spironolactone. The observation period is too short (3 months) to judge whether the other symptoms will improve.

I gratefully acknowledge the helpful interest and advice of Prof. J. G. G. Borst, M.D., Dr. Gowenlock, Dr. J. de Graeff, Dr. Neher, and Dr. H. A. W. M. Tiddens.

University Children's Department
under the care of Prof. W. K. Dicke, M.D.,
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Utrecht, Netherlands. ELISA M. DESMIT.

ABSORPTION, EXCRETION, AND RETENTION OF STRONTIUM BY BREAST-FED AND BOTTLE-FED BABIES

SIR,—The very interesting and important paper by Miss Widdowson and her coworkers [1] was commented on by Dr. Loutit.[2] While there can be no argument with the observations, the original paper contains predictive statements that appear to me misleading in the light of our previous knowledge of strontium metabolism, and warrant further comment.

Miss Widdowson and her colleagues measured the intake and excretion of calcium, strontium, and phosphorus of breast-fed and bottle-fed babies on the 6th, 7th, and 8th day after birth. They state: "If the whole skeleton of the newborn baby contains 5 mg. of strontium, and if breast-fed babies continued to lose strontium at the rate observed over the short period of this investigation (20 μg. per kg. body-weight per day), then in less than 3 months they would have no strontium left inside them. The rate of loss would no doubt decline as the amount in the body fell, but this calculation illustrates the quantities involved"; "If the specific activity in the baby's body is the same as, or higher than, the activity in the mother's milk, then the negative balance for stable strontium makes it unlikely that any strontium-90 will be retained so long as the baby is fully breast-fed"; and "All the breast-fed babies excreted more strontium than they ingested. If the excretion had continued at the observed rate, then in about 3 months they would have had no strontium left in them". These statements leave the impression that breast-feeding would be expected to remove most of the stable and radioactive strontium present in the baby's body at birth, and prevent further deposition during the period of breast-feeding. For reasons discussed below—more fundamental than objections to extrapolation from a short-term balance—I think it is most likely that the strontium/calcium ratio in the baby will reach a steady state, and will always reflect the strontium/calcium ratio in the diet.

We propose the following model as an alternative and, we think, more realistic extrapolation of the observations (support for the values of discrimination against strontium in favour of calcium can be found in many papers [3]). A newborn baby should have a strontium/calcium ratio about one-half that in the mother's circulating fluids because of fœtal discrimination in the passage of the 2 elements across the placenta. The mother's milk should also contain a strontium/calcium ratio about one-half that of her circulating fluids because of mammary discrimination. Thus about the same strontium/calcium ratio would be expected in the body of a newborn

1. Widdowson, E., Slater, J., Harrison, G. E., Sutton, A. *Lancet*, 1960, i, 941.
2. Loutit, J. F. *ibid.* p. 1448.
3. Comar, C. L., Wasserman, R. H. Annotated Bibliography of Strontium and Calcium Metabolism in Man and Animals. U.S. Department of Agriculture, Miscellaneous Publication no. 821, 1961.

baby and in the breast milk of the mother, assuming that the mother's diet has not changed since fœtal calcification started. These statements are supported by the average values Miss Widdowson quotes for $\frac{\text{strontium} \times 10^3}{\text{calcium}}$ of 0·19 for British babies, and 0·2 she found for the breast milk in the study.

In the 6-day-old baby, new bone is being formed, and also parts of the bone are in contact with the circulating fluids so that ion-exchange and remodelling occur. The strontium/calcium ratio in the new bone and in the " exchangeable " part of bone should become approximately equal to the strontium/calcium ratio in the circulating fluids, since in movement between blood and bone there is little or no discrimination. The ratio in the circulating fluids will be governed by that in the diet, by any contributions from bone, and by the discriminatory processes operating. There are no definitive data for the comparative retention of calcium and strontium in young infants, but Dr. Loutit's analysis [2] of Miss Widdowson's data indicates an absorptive discrimination of about twofold for the breastfed baby, and considerable renal discrimination. In any event, it appears that the baby does discriminate against dietary strontium, and a tentative factor of four as in adults would not be an unreasonable basis for discussion, though the true value may be lower, nearer to two.

All this means that in the body of the baby at birth the strontium : calcium ratio will be higher than that which will accrue from the breast milk. Obviously, the exchangeable part of bone will give up some of its strontium to the circulating fluids as it attains its new strontium : calcium ratio, and the resorbing areas will also contribute to an increased strontium/calcium ratio in the circulating fluids. Thus the strontium/calcium ratio in the urinary and endogenous excretions would be increased; and this could logically produce a loss of strontium from the body in the early days of breast-feeding, at least until a steady state was attained between the skeleton and the diet.

Thus it does not seem possible that " in about 3 months the babies would have no strontium left inside them ". Rather, I predict the strontium/calcium ratio of the baby will become, let us say, about one-fourth to one-half that of the dietary ratio, and thus for the study reported attain a value of about 0·05 to 0·1. These comparative ratios would also be valid for strontium-90 to the extent that steady-state conditions are now approximated because of the relatively slow rate of change of strontium-90 in diets over the past year.

It is surprising to note how closely the theoretical strontium/calcium ratios agree with actual observations. For example, Miss Widdowson's data give an average value for adult diet of 1·6; discrimination by the usual factor of four would give an expected value of 0·4 for a mother's circulating fluids; and the expected value for lactation discrimination gives 0·2 for breast milk, which is as reported. Examples of this approach including a sample calculation for breast-feeding were reported by Comar and his colleagues.[4]

Most important was the demonstration by Miss Widdowson and her coworkers that strontium retention was higher in babies fed cow's milk; they attributed this to the increased intake of phosphate with cow's milk as compared with breast milk. Undoubtedly phosphorus may be involved, as has been shown—though not as dramatically—in studies on rats.[5] We feel, however, that besides the stoichiometric strontium/calcium relationships (cow's milk normally having a higher strontium/calcium ratio than mother's milk), and phosphorus intake, other factors should not be overlooked—e.g., calcium intake, calcium/phosphorus ratios, the high lactose content of mother's milk, feeding level, and other chemical differences.

Clearly, the above is an oversimplification. Full explanation of the data does not seem possible, particularly in view of the different behaviour of strontium in babies on 2 different cow's milk preparations, which were alike in calcium and phosphorus content; also the large difference in calcium retention (and presumably new bone formed) between the breast-fed and bottle-fed babies makes the interpretation of the strontium-retention figures difficult. Especially needed are data on diets actually consumed and milk produced by individual mothers, and on intake, and retention, in babies of various ages under conditions where the steady state is approached, so that the strontium heritage of the baby as an important contributory factor can be estimated or eliminated.

Department of Physical Biology,
Cornell University,
Ithaca, New York. C. L. COMAR.

4. Comar, C. L., Russell, R. S., Wasserman, R. H. *Science*, 1957, **126**, 485.
5. Wasserman, R. H., Comar, C. L. *Proc. Soc. exp. Biol., N.Y.* 1960, **103**, 124.

PARENTERAL STEROID THERAPY

SIR,—Parenteral therapy should obviously be avoided when oral administration can be used. Steroids can usually be given satisfactorily by mouth provided proper precautions are taken.

Gastric complications are the commonest; therefore prednisolone should be crushed and taken with food, or at least with milk; and an antacid may also be advisable. These precautions will usually prevent dyspepsia. Enteric-coated tablets are even more effective, though much more expensive. Occasionally even these cause gastric symptoms; yet steroids may be essential. In these cases parenteral administration is worth trying.

5 patients with severe dyspepsia, even when taking enteric-coated prednisolone, have for over six months received weekly intramuscular injections of prednisolone trimethyl acetate (' Ultracortenol ') 200 mg. in 3 ml. This dose seems to be equivalent to 7·5–10 mg. of prednisolone daily. 2 had systemic lupus, and 3 rheumatoid disease; 2 of them had had hæmatemeses.

With parenteral ultracortenol dyspepsia was less severe. This preparation seems useful where serious gastric symptoms still arise even though the prednisolone is enteric-coated.

Royal National Hospital for
Rheumatic Diseases, Bath. GEORGE KERSLEY.

MALARIALS IN ALLERGY

SIR,—I read with interest the article by Dr. Sidi and Dr. Reinberg [1] on the treatment of urticaria with amodiaquine, the letter from Professor Dodds,[2] and the annotation on amodiaquine.[3]

From 1952 onwards we have given mepacrine (' Quinacrine ') and chloroquine for severe bronchial asthma.[4 5] 32 cases were treated over a long period, and 17 of them for one year. 75% improved in varying degrees, and in 53% improvement was considerable. None took place in the first two or three weeks; and most of the cases relapsed some months after the treatment was discontinued.

Since in bronchial asthma considerable placebo effect and a tendency to spontaneous improvement can be expected, no definite conclusions can be drawn from the effect of these preparations until a control series has been studied. But our impression was that their effect was favourable, and the results justify testing them and related drugs further. An experimental basis for this is provided by Genazzani and Javicoli [6] and Geschickter.[7]

Dermatitis was noted during treatment in 6 out of 32 patients, being mild and localised in all but 1 case. In 2 patients there were transient mental disturbances. No arrhythmias were observed. Vega Diaz [8] found mepacrine useful for treating paroxysmal tachycardia. Possibly mepacrine is the drug of choice in patients in whom amodiaquine alters the cardiac rhythm.

Medical Department,
Rogaland County Hospital,
Stavanger,
Norway. ARNFINN ENGESET.

1. Sidi, E., Reinberg, A. *Lancet*, 1960, ii, 842.
2. Dodds, E. C. *ibid.* p. 930.
3. *ibid.* Feb. 4, 1961, p. 268.
4. Engeset, A. *ibid.* 1952, ii, 537.
5. Engeset, A. *Nord. med.* 1958, **58**, 1492.
6. Genazzani, E., Javicoli, I. *Boll. Soc. ital. Biol. sper.* 1951, **27**, 1348.
7. Geschickter, C. F. *Sth. med. J. Bgham, Ala.* 1955, **48**, 497.
8. Vega Diaz, F. *Brit. Heart J.* 1950, **12**, 132.

Obituary

JULIAN TAYLOR

C.B.E., M.S. Lond., F.R.C.S., Hon. F.R.A.C.S.

BY precept, principle, and practice Julian Taylor proved himself a superb teacher of surgery (and other things) in places as diverse as a great London teaching hospital, a Japanese prisoner-of-war camp, and the medical school of the Sudan. In each he gave his students of his best and successfully insisted that they should give of theirs.

He was born in 1889 and was educated in London at University College School and University College Hospital, qualifying in 1911. His span as a working surgeon was exceptionally long. In 1914 there appeared in the *London Gazette* that unique entry "R.A.M.C. L/Cpl Taylor, J., F.R.C.S., to be Lieutenant", and a few months later he was at work as a surgeon in the Expeditionary Force. Later, posted with his unit to Salonika, he was transferred to a general hospital and became officer in charge of the surgical division. He returned to University College Hospital, and after a spell on the professorial unit was elected to the staff. He also joined the staff of the National Hospital, Queen Square, and of the Harrow Hospital.

In the late war he went back to the R.A.M.C. and served in the Malayan Command. After a few weeks he was taken prisoner, and, already in his fifties, he spent the next years in Changri camp. For his work there he was appointed C.B.E. in 1946. When he returned to London he set to work again in his hospitals, and he served as vice-president of the Royal College of Surgeons. But he seemed not to care much for the effort to establish again a large consulting practice, and in 1954, he retired at the age of 65. But he was still prodigal of his power to work and to teach, and soon afterwards he accepted the post of professor of surgery in the University of Khartoum. He at once began to establish in the Sudan a training centre for surgeons in accord with the traditions and practice of British surgery; and through his initiative the examination for the primary F.R.C.S. has been held for the past two years in Khartoum. He also applied his energies to the surgical problems of the Sudan. His investigations included the epidemiology of hydatid infection and the treatment of Madura foot. In the last two years despite a serious failure of health he carried on with his work. Almost his last act was to invite two young Sudanese students to stay with him when he came on leave. Two days after his return, on April 15, he died at his country home at Bepton while discussing further measures to help the development of surgery in the Sudan.

Even this bare outline of his career shows that Julian Taylor was no ordinary man. But only those who worked with him can fill the gaps. A colleague, who was once his student, writes:

"Those who know University College Hospital will see in Julian's life something of an extension of Wilfred Trotter's thought and action. But there was much more than this; as the years unfolded bringing their successes and adversities Julian pursued his way outwardly unperturbed, encouraging, guiding, and teaching the young men and women who were about him in ways of thought and practice which he had matured. In his selection of these youngsters he had an unerring judgment of the mediocre, the insincere, the superficial; and these few failed. He saw good in many who were seemingly rebels against orthodoxy, finding in them the tinder of originality. He would defend these men and draw them on, and was not infrequently rewarded.

"Throughout his life he was more interested in solving the problems of his patients than in amassing large numbers of 'cases'—a word he abhorred. He scorned the impersonal approach to clinical work and maintained that more could be learnt by careful observation of a few patients than by a detached study of a multitude of statistics. His delight was to piece together from small points of history and examination the answer to some difficult diagnostic problem, perhaps later to be verified with glee in the operating-theatre. There with hands that were never gentler nor more precise and yet swift, he was a master of simplicity in technique and the avoidance of all fuss.

"He matured in an era when a surgeon could be more catholic in his endeavours than is now readily possible, and it was no problem for him to succeed in widely divergent spheres of surgery. He approached all problems from simple first truths and held that these were the key to understanding and management. Thus, he held, should all surgeons begin, and where their interest took them later was a matter for the future and circumstance to decide. But with the increasing complexity of some surgical advances he conceded the necessity of specialisation, provided always that the young surgeon's foundations were both wide and firm.

"To some Julian Taylor may have seemed difficult to know. He had a personal reserve of manner which they felt was a barrier to be surmounted. Behind this could be found a gentleness of nature and a sympathetic understanding of others accompanied by an immense firmness of purpose and self-discipline. He had a deeply considered philosophy and surveyed the world around him with a sharp but delicate wit. Yet he was never overtly angry. If he rebuked, it was with a quietness and precision that made the recipient think and mend his ways. Julian's poise was never lost, his calm dignity was impregnable."

Of the years at Changri J. W. D. B. relates:

"The primitive, overcrowded prison hospitals contained many battle casualties and the fact that so many survived was in no small measure due to Julian Taylor's efforts and advice. In the 1914–18 war he had gained valuable experience, but his greatest quality was his all-round knowledge of surgery. Most general surgeons of today would have been lost in the chest or nervous system or in orthopædics, but Julian Taylor's training under Trotter had made him as much at home in the brain as anywhere else, and he was able to tackle anything from the top of the head to the soles of the feet. One great problem he overcame was the rehabilitation of those who had lost a lower limb, particularly the above-knee amputations. With the aid of a sapper officer he designed and built limbs with beautiful knee-joints—no easy task, for the geometry is not as simple as might appear—which functioned remarkably well. These limbs were inevitably heavy, for they were hewn from the local wood, but they served their owners well. Another surgical triumph was Taylor's tackling of pyloric ulcers in appalling surgical conditions—an emaciated patient, no X-rays, only chloroform for anæsthesia, and no milk for the immediate postoperative period.

"His presence in the prison camps was a constant inspiration to us all. It was not only his surgical skill, but his stimulating and critical approach to any problem. He had a wide range of interests, and we younger men looked on him rather as a senior don on whom we could drop in at any time to discuss any topic."

J. A. F. also gratefully remembers Taylor's generosity as a teacher at Changri:

"Throughout those three and a half years Taylor continued as a matter of course to teach any medical man who had a will to learn, but he also worked constantly in the important task of keeping alive men's interests in a large variety of subjects. A man of wide culture, he would give courses of lectures on English history, French history, or isolated talks on sailing, navigation, the tides around the English coasts, or on the lesser-known alleyways of the City of London. All such lectures, enlivened by his spicy wit, helped to support men's hopes and—especially when times were bad—to dispel despair. When most of us could not see the wood for the trees, he would stand back and point out what was most needed of us. In private circles one heard his wit turned on ourselves and

best of all upon the various personages of the Army hierarchy. How he loathed pomposity, and what a sharp nose he had for insincerity or humbug: and all this from a quiet modest personality (he hated being saluted) who was always approachable and ready to help the most humble ward-orderly."

J. B. L., who shared Taylor's work in the Sudan, writes:

"Though at times he had a satirical turn of phrase, those who knew him well realised that he had a keen appreciation of his own few foibles and a wonderful humility. To work and live with him, whether in Khartoum or on trek in the Sudan, was an education never to be forgotten. To the end of his life he never considered retirement; in his final illness he discussed enthusiastically the furtherance of his plans for the development of surgery in the Sudan and for research work in the serious problem of maduromycosis."

C. W. F. sums up his qualities as a surgeon and a man:

"Julian Taylor's virtuosity and skill as a surgeon were staggering. He did too much too well to establish a specialised reputation. To the end of his career at U.C.H. he was undertaking operating-lists of great diversity which were the envy and despair of his younger colleagues. Perhaps the finest testament to his greatness as a surgeon is the chapter he wrote on surgery in Changri prison camp in the *Official History of Surgery in the Second World War*. There is set out, with statistical tables, an analysis of the kind of work done by him and under his direction under appalling conditions, with inadequate resources, producing results which would be considered satisfactory by any standard. Only by superb skill or profound artistry could such results have been achieved, and Julian had both. To read that chapter is a humbling experience.

"To young men and women in the profession he gave without stint friendship and encouragement. He was kind without limit to generations of students and house-officers, and yet he was armoured with an inner reserve that made it difficult to know him well. Many who had received at his hands help and encouragement, often of the most practical kind, who loved and admired him, felt a measure of sadness that he seemed to need so little in return. Others who knew him less well were rebuffed by his reserve, or were put off by his impish and often sharply worded refusal to be impressed by pomposity or platitude.

"Latterly we saw him only on his leaves from the Sudan, still young-looking, still impish, still kind. He knew his life was precarious: he did not try to husband it. For the manner of his death, his friends and pupils can feel no sadness: for the example of his life they are for ever in his debt."

Mr. Taylor married in 1926 Margaret Ross-Johnson. She died in 1955, and they leave two sons.

A memorial service will be held on Wednesday, May 10, at noon at St. Pancras Church.

ERNEST TERTIUS DECIMUS FLETCHER

M.A., M.D. Cantab., F.R.C.P.

Dr. Ernest Fletcher, consulting physician to the Royal Free Hospital, London, died on April 16 at the age of 69.

He was born in London, the younger son of the late Prof. Banister Fletcher, F.R.I.B.A. From Wellington College he went to Magdalene College, Cambridge. During the 1914–18 war he served as a brigade machine-gun officer with the 8th Mounted Brigade. He had already begun his medical studies at St. Bartholomew's Hospital, and in 1918 he returned to this country to qualify. After serving a year with the R.A.F. Medical Service he was demobilised, and later he held house-appointments at St. Bartholomew's Hospital.

Soon after the war he joined the staff of the Queen Mary's Hospital, Stratford, the Italian Hospital, and the St. Marylebone General Dispensary. In 1938 he was appointed assistant physician, and later physician to the rheumatology department of the Royal Free Hospital. During the late war he was physician in charge of a medical division under the E.M.S.

In the years before the war rheumatism had become his chief medical interest, and in 1939 he was elected Heberden lecturer and medallist. He was consultant to the Charterhouse Clinic. He was also a member of the Empire Rheumatism Council and he was president of the Heberden Society in 1956–57. In his book on *Medical Disorders of The Locomotor System*, first published in 1946, with his collaborators, he put forward the view that the anatomy, physiology, and pathology of the locomotor system could be a basis for specialised medical as well as surgical practice. He was a consulting editor of the *Postgraduate Medical Journal*. He was elected F.R.C.P. in 1954.

F. D. H. writes:

"Ernest Fletcher was well known not only to his colleagues of the Royal Free Hospital but to all interested in the study and treatment of rheumatic disorders. He was a friend of the late Lord Horder; though the two men had outwardly little in common, they thoroughly enjoyed each other's company and both enjoyed each other's sense of humour. For the past few years Ernest Fletcher had not had good health, but he bore his troubles philosophically and uncomplainingly."

F. L. L. writes:

"Dr. Fletcher expanded the rheumatology department at the Royal Free to make it one of the best in London. Under his direction a laboratory was set up and considerable work done in it, especially in the serological tests for rheumatoid arthritis.

"Ernest Fletcher was fond of banter and light conversation, and he was an excellent host and a charming companion. In later years he suffered a good deal of ill health some of which was not without its blessing, for he was forced to take a prolonged holiday in the mountains of Wales during which he wrote his lucid textbook on rheumatology. Recognition came to him late in life and was all the more appreciated by him because of this."

Dr. Fletcher had two sons by his first marriage. He is survived by his second wife.

WILLIAM STANLEY SYKES

M.B.E., M.A., M.B. Cantab., D.P.H., D.A.

AT the age of 67 Dr. Stanley Sykes died suddenly on March 31.

Born at Morley, he was educated at Rossall and at Emmanuel College, Cambridge. During the 1914–18 war he served in the Navy both before and after qualifying from St. Bartholomew's Hospital. After house appointments at Bart's, he entered general practice at Morley, but also worked as an anæsthetist to Leeds General Infirmary and other hospitals. In 1927 he produced his *Manual of General Medical Practice*, and in 1931 his first book on anæsthetics appeared in the Modern Treatment Series. As a relaxation he also wrote thrillers, one of which, *The Mystery of the Missing Money Lender*, has appeared as a Penguin.

During the second world war he was attached to the 26th General Hospital as anæsthetist in the rank of major. Captured in Greece, he was a prisoner for $4^1/_2$ years; but "he was by no means idle during this period, practising his anæsthesia under most difficult and primitive conditions, administering a hospital, and inspiring his junior colleagues". At the end of the war he was appointed M.B.E.

On his return to Leeds, a difference of opinion with the board of governors led him to give up anæsthetics and go back to general practice. He retired two years ago but was busy on his chief book—*Essays on the First Hundred Years of Anæsthesia*. Judging by the first volume, which we reviewed on July 23 last, this is both a scholarly and a very readable work, and the volumes to be published posthumously will be awaited with real interest.

Dr. Sykes leaves a widow and a stepdaughter.

ALEXANDER MILLAR MEEK GRIERSON

O.B.E., M.D. Edin., D.P.H., F.R.S.E.

Dr. Grierson, deputy medical officer of health for Manchester, who died on April 13, was a son of the late Sir Andrew Grierson and graduated in medicine at Edinburgh in 1923.

Choosing public health as his career, he took a post in the bacteriological department of the university before appointment to the public-health department of the city. In 1935 he was appointed Manchester's senior medical officer for housing, and worked hard and happily under the late Dr. Veitch Clark. During the war, when the housing programme was suspended, he was concerned at first with air-raid precautions and later with medical control after the heavy raids on Manchester, particularly in 1940. For this work he was appointed O.B.E. After the war, he was senior medical officer in general administration, and in 1947 he succeeded the late Dr. W. St.C. McClure as deputy medical officer of health.

" He had a flair for administration," writes C. M. B. " The problems of the aged and infirm were one of his first cares, and his reputation for his wise and gentle handling of these cases was widely recognised. His integrity was complete and invincible and for his great unstinted loyalty I personally have had much reason to be grateful. The officers of the department, senior and junior alike, found him approachable and kind."

Dr. Grierson, who was 59, is survived by his wife.

J. C. PROSSER-FRENCH

L.D.S.

WITH great regret we record the death, at 46 years of age, of " Jay " Prosser-French, a member of the editorial staff of *The Lancet* since last September. He died on April 10 after a few days' illness.

Educated at Tonbridge School, he qualified in dentistry from Guy's Hospital in 1936. After some years in private practice, he joined the London County Council's school dental service in 1949, and in 1957 he went to Luton, where he later succeeded to the post of principal school dental officer. For a man who was not only sensitive and retiring but also in precarious health, the care of children in dental clinics was a continuing strain; but " I get more satisfaction from this public-health work ", he said, " than from anything I have done before ".

To medical journalism he brought unusual talents, whose value became evident only slowly. As was obvious to all who knew him, he was one of those people who can make any machine or gadget work. But, unlike so many practical mechanics, he was also a serious student of science, whose perpetual curiosity about causes and effects led him to read widely and remember what he read. His motor-car for many years was characteristic: bought for a song, it contained every device one could think of, from altimeters downwards. Equally characteristic was his special knowledge both of clocks and of horology. He was happy in restoring function, and no doubt it was the manifold ingenuities of dentistry that attracted him to that profession. In the evening, when other people might read a novel, he would prefer a book on electronics or genetics; and increasingly he enjoyed writing, both as another craft to master and because it led him into fresh exploration of fact and theory. He had at home a large collection of technical works and his information was carefully organised. His mind was in fact so far academic that he ought to have spent his life in research rather than practice. But work for a medical journal gave him some of the mental exercise he enjoyed; and he had made an important place among us. We gradually came to recognise his intellectual energy and the remarkable range of his knowledge, while his patience and unassuming gentleness won our affection from the first.

He married Miss F. F. Lewis, and they have a daughter.

Mr. HAMILTON BAILEY

H. D. writes:

" In 1920 Hamilton Bailey left the eclectic atmosphere of the London Hospital to galvanise that of Liverpool Royal Infirmary as surgical registrar. His teaching brought enlightenment to the students and success to its postgraduates in the final fellowship, and in 1923 he was elected to the staff. In those days a surgical firm had 50 beds, of which the assistant surgeon had 2 courtesy beds. Hamilton Bailey obtained his surgical experience from emergencies and assisting the Chief twice a week. After a year or so of this comparative inactivity, though he obviously stood a good chance for the professorship in 12 or 14 years' time, to everyone's astonishment he resigned his post for a more active surgeoncy at Dudley Road Hospital, Birmingham. His action, with that of Huddy, also a first assistant from the London Hospital, was one of the early steps in the upgrading of the board of guardian hospitals. In Birmingham Bailey did a tremendous amount of operative work and completed the first edition of his classic *Physical Signs in Surgery*, which was an immediate success. After his return to London his writings, surgical work, and new operations, such as the total excision of the parotid gland, surged forth in a steady torrent. Moreover, his writings were of an arrestingly high quality, which, together with the illustrations, set a new standard in medical publications. He had a gift of the epic phrase, such as ' A low tracheotomy is a deep, dark and dangerous bloody operation ', or ' The renal artery may slip and be like a kicking fish in a deep pool '.

" As a grateful pupil and friend, I think that we shall remember Hamilton Bailey as an author of beautifully illustrated writings, an ingenious surgeon, a great teacher, and a lovable man."

Dr. IVAN McCAW

F. M. B. A. writes:

" Dr. McCaw was one of the most charming personalities of medical life in Belfast. The handicap of a severe war injury deprived him of his ambition to be a surgeon, but it was responsible for his taking up dermatology, and he initiated a service in Northern Ireland which was to become known internationally and to attract a number of colleagues who will continue where he has left off. Ivan was one who enjoyed company and a quiet unostentatious social life; golf was one of his happiest recreations and at which (despite his injury) he was a very good performer, as many of us who played with him know. His was a happy disposition, and when committee meetings became contentious he had always a quick conciliatory word, and often a light remark which resolved lack of harmony."

Prof. J. M. SMELLIE

F. M. B. A. writes:

" James Smellie's standing amongst his colleagues was very high and his gift for friendship was outstanding. As one who knew him for a long time I came to appreciate his qualities more and more, and also to enjoy his companionship and hospitality. He had a sound critical appreciation of a problem, whether it was clinical or administrative, and his opinion, expressed in a few sentences, was always respected and usually acted on. He is certainly a great loss to pædiatrics and to the Birmingham Medical School."

Appointments

DACRE, A. J. I., M.B. Lond.: consultant psychiatrist, Rampton Hospital, Retford, Notts.

HAMILL, JOHN, B.M. Oxon., F.F.R., D.M.R.D.: consultant radiologist, United Oxford Hospitals.

MACCALLUM, F. O., M.D. Toronto, M.R.C.P.: consultant bacteriologist, Radcliffe Infirmary, Oxford.

ROHAN, T. M. B., M.B. N.U.I., D.P.H.: M.O.H., Guisborough, Yorks.

ROWLING, J. T., M.D., M.CHIR. Cantab., F.R.C.S.: part-time consultant surgeon, United Sheffield Hospitals.

THOMAS, M. L., M.B. Cantab., M.R.C.P., D.M.R.D.: assistant radiologist, X-ray diagnostic department, St. Thomas's Hospital, London.

WRIGHT, W. B., L.M.S.S.A., D.P.M.: consultant psychiatrist and deputy physician-superintendent, Royal Scottish National Institution, Larbert.

Notes and News

WORD BLINDNESS

AT a meeting of the council of the Invalid Children's Aid Association in London on April 17, Dr. A. WHITE FRANKLIN, from the chair, explained that the Association has moved from its primary interest in physical environment to the problems that arise because a child cannot adjust to school life. Word blindness had come to be recognised as a block in the learning machinery, arising independently of other handicap, and it seemed important that all the sufferers should be recognised and given treatment.

Dr. MACDONALD CRITCHLEY started from the problem of the slow reader. At one end of the scale was the dull child, and at the other the intelligent but neurotic child, while somewhere in the middle was a hard core of cases which he regarded as having a genetically determined developmental error. He described three cases: a boy of 13 who was bright but because he could not read climbed on a live rail and was electrocuted; a nurse of 21 who had had a long series of troubles whose cause had never been recognised; and a boy of 10 who was good at arithmetic but showed signs of serious frustration. Progress in recognising and treating these cases was greater in Scandinavian countries than in England, although James Kerr, working as a school medical officer in London in 1896, had been the first to draw attention to the condition. No figures were available for England, but in Denmark 10% of children attending school were said to have some degree of word blindness. This high figure might be due to a gene difference.

Dr. Critchley thought that the syndrome which he recognised was best known as developmental dyslexia. He found that some affected children were bad at arithmetic but many very good—especially at mental arithmetic. Many had a difficulty about handedness, but he thought that a dominance of one lobe could be found if careful examination were made. There was crossed laterality at times, but in about half the cases disorientation on the patient's attempts to diagnose left from right. There was also hesitation over selecting a finger on request (finger agnosia). The prognosis depended on recognition: with great patience the majority could be taught to read, and even to read quite quickly and for pleasure. They never wrote well nor did they spell correctly. Writing and spelling errors followed a recognisable pattern, and from the state of the manuscripts of Hans Christian Andersen it seemed certain that he suffered from the condition. One of the most serious complications was behaviour difficulty, and at times delinquency or even suicide, through the frustration experienced during education and later in life.

Dr. J. N. HORNE, of the Ministry of Education, referred to a survey of dyslexia which he is conducting. A request had been made through the country for names of severely backward readers, and out of 600, 120 had already been seen. I.Q.s ranged from 85 to 149: below 85, cases were not accepted. Dr. Horne distinguished two categories: (1) a reading delay in children of average intelligence without obvious physical or emotional handicap, and (2) true developmental dyslexia where the child fails to respond to ordinary teaching methods. In the former group the delay had to be not between reading and calendar age but between reading and mental age. A two-year gap was relatively common but significance should be attached to a three-year difference. In considering these cases it was important to be sure about other possible causes of delay. For example, vision was usually not tested before the age of 7, and for two years the child might have a disability that went unrecognised. If there was any reading delay a near-vision test should be done at once. Poor concentration was often the result of an emotional disturbance, but serious emotional disturbance commonly resulted from developmental dyslexia. His figures suggested that the incidence of crossed laterality had been exaggerated. Speech defects had to be remembered as playing their part.

Mrs. ARKELL described the work of the Word Blind Institute in Copenhagen. She thought that only 1% of Danish schoolchildren were handicapped severely enough to need treatment. The children attended normal school but had one lesson daily at the institute, and Danish schoolteachers were trained in the special methods used.

The discussion which followed was concluded by a schoolteacher who put the case of those who regard dyslexia as nothing more than a severe form of slow reading associated with emotional disturbance.

ROCKEFELLER GRANTS FOR AFRICA

DURING the first quarter of 1961 the Rockefeller Foundation made grants of over 3 million dollars. Those for medical and natural sciences amounted to over 1 million dollars.

A grant of £50,000 is to be made over the next five years to the London School of Hygiene and Tropical Medicine to help meet the expenses of an investigation into bilharziasis in the Lake Victoria region of Africa. Studies of various aspects of human and animal bilharziasis and of the snails that maintain it are already under way in a number of African institutions. The London School will coordinate these different projects, and a collaborative research team in Africa will conduct studies of the clinical disease in communities as well as among hospital patients, study the ecology and biology of the snails of the region, and correlate the incidence of chronic disease with bilharziasis. In London the Ross Institute will undertake basic biological studies of the snail host and of the different species of the parasite. The institutions cooperating with the London School are the Makerere College, Kampala, Uganda, which will serve as the base for the clinical work, and the East African Medical Research Council, whose personnel will form the core of the field staff. The World Health Organisation is expected to provide a statistician for the team, and to use the African unit as an orientation and training centre for its own personnel as well as for African scientists.

A five-year grant of £10,000 is being made to support University College, Ibadan, Nigeria, which is initiating a faculty exchange programme with the medical schools at Dakar, Leopoldville, Khartoum, and Kampala. The exchange programme will be under the direction of Prof. Alexander Brown, head of the department of medicine at Ibadan. Two visitors from each of four of the schools are to spend annually a minimum of two weeks at the fifth faculty. Each year a different school will serve as host for eight professors, two from each of the four other participating schools.

Royal College of Surgeons of England

Faculty of Anæsthetists.—A scientific meeting on hypothermia is to be held by this faculty on Saturday, May 6, at 10.30 A.M., when the speakers will be Prof. Eric Neil, Mr. C. E. Drew, Mr. L. S. Walsh, Dr. David Mendel, and Dr. P. Cliffe.

Faculty of Dental Surgery.—A scientific meeting on temporomandibular joint problems and their treatment is to be held by this faculty on Saturday, June 3, at the college, Lincoln's Inn Fields, London, W.C.2. Further particulars may be had from Mr. R. S. Johnson-Gilbert, secretary of the faculty, at the Royal College of Surgeons.

Royal College of Surgeons in Ireland

Faculty of Anæsthetists.—The following elected fellows will be admitted to the faculty on June 3:

H. E. Bell, G. W. Black, J. K. Black, A. Blayney, J. P. Conroy, C. F. Cuniffe, B. J. Daly, I. Davidson, E. J. Delaney, D. Donovan, P. A. Forster, J. D. Gaffney, W. R. Gilmore, A. J. Haley, S. Hoffmann, N. Jafry, W. R. Lamb, P. V. Lang, J. G. Lomaz, J. Lynham, L. McArdle, J. McAuley, P. McGarry, I. D. Michie, W. F. K. Morrow, C. Moss, S. P. Murphy, A. O'Connor, K. P. O'Sullivan, A. Owen-Flood, J. Ozinsky, F. W. Parke, S. Poonambalam, Y. K. Poon, D. Power, M. Prosad, J. R. Radcliff, H. Raftery, O. Schmahmann, D. Verley, R. D. Walsh, K. H. Wayburne, F. de Burgh Whyte, D. S. Wilson.

Association of Anæsthetists of Great Britain

This Association is offering three prizes for papers based on research in anæsthesia or related subjects. Entrants need not be members of the Association. Full details may be had from the hon. secretary of the Association, 47, Lincoln's Inn Fields, London, W.C.2, to whom entries must be sent on or before March 30, 1962.

Society for General Microbiology

For the forthcoming year the officers of this society are: President, Prof. R. Lovell; treasurer, Prof. K. E. Cooper; editors, Prof. B. C. J. G. Knight and Mr. A. F. B. Standfast; meetings secretary, Dr. B. W. Lacey; general secretary, Dr. S. T. Cowan.

The subject of the society's symposium in 1962 will be microbial classification.

The Psychotic Child

The National Society for Mentally Handicapped Children is to hold a conference on this subject on Friday, May 5, at the Cowdray Hall, Henrietta Place, London, W.1. The medical speakers will include Dr. Gerald O'Gorman, Dr. Mildred Creak, and Dr. Kenneth Soddy. Application forms may be had from the conference secretary of the society, 125, High Holborn, London, W.C.1.

British Epilepsy Association

The annual general meeting of this Association is to be held on Thursday, May 4, at 3 P.M., at the Clothworkers' Hall, Dunster Court, London, E.C.3.

British Spas Federation

Dr. A. P. H. Randle will give a Lord Horder prize lecture on Wednesday, May 3, at 5 P.M., at the Town Hall, Leamington Spa. He will speak on medicosocial problems of rehabilitation.

British Association for the Advancement of Science

The annual meeting of this Association is to be held from Aug. 30 to Sept. 6 in Norwich, under the presidency of Sir Wilfrid Le Gros Clark. Further particulars may be had from the secretary of the Association, 18, Adam Street, London, W.C.2.

British Association of Physical Medicine

The annual dinner of this Association, which is now 18 years old, was held on April 21 at Apothecaries' Hall in London.

Prof. H. J. Seddon, president of the British Orthopædic Association, spoke with pleasure of the growth of physical medicine (though there is still much room for expansion in the North of England), and of the closer links being formed, to mutual advantage, with orthopædic surgeons. Dr. Hugh Burt, the president, thanked Professor Seddon for his large part in encouraging physical medicine. He welcomed Dr. George Godber as chief medical officer of the Ministry of Health, and referred to Dr. Philippe Bauwens' recent outstandingly successful tour of the United States.

Dr. R. M. Mason proposed The Guests, and Prof. A. C. H. Bell, president of the Royal College of Obstetricians and Gynæcologists, responded.

Alexander Society

Mr. A. Rugg-Gunn will give an F. Matthias Alexander lecture on Tuesday, May 2, at 6.30 P.M., at 11, Chandos Street, London, W.1. Its title will be Physiological Gradients.

A symposium on tracheostomy and artificial respiration is to be held by the University of Cambridge Postgraduate Medical School on Saturday, May 27, at 10.30 A.M., at Addenbrooke's Hospital, Cambridge. Further particulars may be had from the secretary of the medical school, Tennis Court Road, Cambridge.

At a meeting of the Medical Electronics Discussion Group on Friday, May 5, at 6 P.M., at the Institute of Electrical Engineers, Savoy Place, London, W.C.2, there will be a discussion on artificial muscles. The opening speaker will be Dr. A. B. Kinnier-Wilson.

A semipermanent exhibition will be held at the Institute of Dermatology, Lisle Street, London, W.C.2, from May 3 to 27, by Dr. Brian Russell and Dr. D. C. G. Bett on dermabrasion.

An exhibition to show the part Bristol played in the evolution of mental health between 1696 and 1961 is to be held from May 4 to 24, at the Royal West of England Academy of Art, Bristol.

The Hospitals' Symphony Orchestra will hold a concert at the Royal Academy of Music, Marylebone Road, London, N.W.1, on Saturday, May 13, at 8 P.M. Admission is by programme obtainable from Robert Tate, Guy's Hospital Medical School, S.E.1.

CORRIGENDUM: *Can the National Health Service Survive?*—We regret that a phrase was omitted from a sentence in the penultimate paragraph of Dr. Seale's letter (April 15, p. 824). The sentence should have read: "Indeed the present structure of the N.H.S. ensures that any withdrawal will quickly turn into a rout, because instead of built-in stabilisers to preserve the balance between the private and public sectors, it contains built-in accelerators."

Diary of the Week

APRIL 30 TO MAY 6

Monday, 1st

UNIVERSITY OF LONDON
5.15 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. L. Lynen (Munich): Biological Pathways to the Carbon Skeleton in Natural Products. (Second of three lectures.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. C. A. Clarke: Application of Genetics to Clinical Medicine.

INSTITUTE OF DERMATOLOGY
5 P.M. (32, Welbeck Street, W.1.) Dr. Paul Strickland: Clinical Effects of Ionising Irradiation on the Skin.

INSTITUTE OF NEUROLOGY
5.30 P.M. (National Hospital, Queen Square, W.C.1.) Dr. E. J. Moran Campbell: Neurology of Respiration. (First of two lectures.)

WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School, W.2
5 P.M. Prof. J. N. Morris: Studies in Cardiovascular Disease. (Almroth Wright lecture.)

Tuesday, 2nd

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Dr. H. E. Lewis, Dr. J. P. Masterton: Polar Physiology—its Development in Britain. (Arris and Gale lecture.)

UNIVERSITY OF LONDON
5.15 P.M. (London School of Hygiene and Tropical Medicine.) Professor Lynen: Biological Pathways to the Carbon Skeleton in Natural Products. (Last of three lectures.)
5.30 P.M. (School of Pharmacy, Brunswick Square, W.C.1.) Prof. Hallowell Davis (St. Louis, Missouri): Principles of Sensory Action. (First of two lectures.)

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Dr. Noel Gosse: Changing Face of Obstetrics.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY, 91, Dean Street, W.1
5.30 P.M. Dr. G. F. Swann: Cases of Neuroradiological Interest.

Wednesday, 3rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1.
5.15 P.M. *History of Medicine.* Dr. A. L. Goodall: Robert Watt, Physician and Bibliographer.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Henry Haber: Skin Changes due to Degeneration in the Corium.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. N. R. Barrett: Bronchial Carcinoma—Send Us the Cases Early!

ASSURANCE MEDICAL SOCIETY
5 P.M. (11, Chandos Street, W.1.) Dr. L. G. Norman: Medical Aspects of Road Safety.

MEDICO-CHIRURGICAL SOCIETY OF EDINBURGH
8.30 P.M. (Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh.) Prof. K. W. Donald: Cardio-respiratory Function in Relation to Clinical Medicine.

Thursday, 4th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5.30 P.M. Dr. R. Bodley Scott: Blood Diseases in Relation to Otolaryngology.

UNIVERSITY OF LONDON
5.30 P.M. (School of Pharmacy.) Professor Davis: From Sound to Nerve Impulses. (Second of two lectures.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
4 P.M. Dr. Moran Campbell: Diagnosis and Management of Respiratory Failure.

ROYAL SOCIETY OF MEDICINE
10.30 A.M. *Otology.* Dr. Howard P. House (California), Dr. I. Simson Hall, Mr. Terence Cawthorne: Present Position of Stapes Footplate Surgery.
2 P.M. *Neurology.* Start of three-day joint meeting with the Società Italiana di Neurologia.
2.30 P.M. *Laryngology.* Mr. A. Young, Dr. Miles Taylor, Mr. P. H. Golding-Wood: Vasomotor Rhinitis. Sir Victor Negus: Observations on the Term Epipharynx.
5.30 P.M. *Anæsthetics.* Dr. R. S. Walsh: Management of Patients in a Respiratory Unit.

NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Hospital, Oxford
8.30 P.M. Dr. Victoria Smallpeice: Growth and Nutrition from the Pædiatrician's Viewpoint.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Prof. M. J. Dallemagne (Liége): Problem of Bone Salts.

Friday, 5th

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. R. S. Lawrie: Carcinoma of the Mouth.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. J. C. Hogg: Nasal Obstruction.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh
3.30 P.M. Mr. A. J. Gardham: Carcinoma of the Mouth.

Saturday, 6th

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
10 A.M. Prof. Otto Lowenstein: Evolution of Static and Acoustic Sense Organs. Professor Davis: Relation of Presbyacusic to Noise-induced Hearing Loss. Dr. Jurgen Tonndorf (Iowa City): Cochlear Hydrodynamics.